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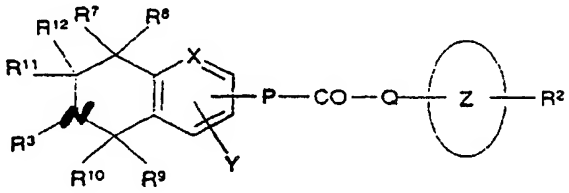

(I)

(57) Abstract

Compounds of formula (I) including tetrahydroisoquinolinyl cinnamides and acrylamides are indicated to be useful for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti–convulsive agents, such as epilepsy including post–traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia and narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

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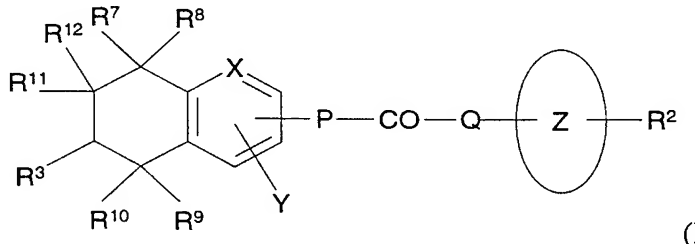
SUBSTITUTED ISOQUINOLEINES AND THEIR USE AS ANTICONVULSIVANTS

This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

It has now been surprisingly found that cinnamide and acrylamide compounds of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Accordingly, the present invention provides a compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

in which

Z is a carbocyclic or heterocyclic or a fused carbocyclic or heterocyclic ring containing at least one aromatic ring;

X is CHor N;

Y is hydrogen, C_{1-6}alkyl, or a halogen;

P is -CH=CH- and Q is $-NR^1-$, or;

P is -CH=CH- and Q is $-NR^1CH_2-$, or;

P is -NH- and Q is -CR^{1a}=CH-;
R^1 ishydrogen, phenylC_{1-6} alkyl, or C_{1-6} alkyl;
R^{1a} is hydrogen, halogen, phenylC_{1-6} alkyl, or C_{1-6} alkyl;
R^2 ishydrogen or up to three substituents selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, CF_3SO_2, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkylO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, C_{1-6}alkylS-, C_{1-6}alkylSO_2-, or 1,3-oxazol-5-yl, $(C_{1-4}alkyl)_2NSO_2$-, $(C_{1-4}alkyl)NHSO_2$-, $(C_{1-4}alkyl)_2NCO$-, $(C_{1-4}alkyl)NHCO$- or $CONR^4R^5$, CO_2R^4;
or -NR^4R^6 or $NHCOR^4$
where R^4 and R^5 are each independently hydrogen or C_{1-4} alkyl, and;
R^6 is hydrogen, C_{1-4}alkyl, formyl, -CO_2C_{1-4}alkyl, or -COC_{1-4}alkyl;
or two R^2 groups are linked together to form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O or a heterocyclic ring that is saturated or unsaturated;
or when P is -CH=CH- and Q is -NR^1CH_2-, R^1 and an R^2 are linked together to form a saturated or unsaturated carbocyclic or heterocyclic ring;
or when P is -CH=CH- and Q is -NR^1-, R^1 and an R^2 are linked together to form a saturated or unsaturated carbocyclic or heterocyclic ring, and;
R^3 is hydrogen, phenylC_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkylOCO-, C_{1-6}alkylCO-, formyl, CF_3CO- or C_{1-6}alkylSO_2-, hydroxyC_{1-6}alkyl, or C_{1-6}alkoxyC_{1-6}alkyl.
R^7 is hydrogen or C_{1-6} alkyl;
R^8 is hydrogen or C_{1-6} alkyl;
R^9 is hydrogen or C_{1-6} alkyl;
R^{10} is hydrogen or C_{1-6} alkyl;
R^{11} is hydrogen or C_{1-6} alkyl, and;
R^{12} is hydrogen or C_{1-6} alkyl.

In the formula (I), alkyl groups, including alkyl groups that are part of another moiety, may be straight chain or branched. Aromatic rings, especially phenyl groups, including rings that are part of another moiety, may optionally be substituted with one or more independently selected halogen, C_{1-6} alkyl, C_{1-6}

alkoxy or C_{1-6} alkylcarbonyl groups. Suitable halo substituents include fluoro, chloro, iodo and bromo. Suitable C_{3-6} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

When ring Z is heterocyclic, Z may be for example furanyl, thiophenyl, indolinyl or indazolinyl. Preferably Z is phenyl.

Linked R^2 groups and linked R^1 and R^2 groups are typically such as to form a 5 or 6 membered ring fused to the ring to which the R^2 groups are appended. Thus when Z is phenyl, the linked R^2 groups or linked R^1 and R^2 groups may create fused rings such that the moiety Q is tetrahydroquinolinyl, tetrahydroisoquinolinyl or dihydroindolinyl.

Preferably a substituent for a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-N-(C_{1-6})alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryloxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-6})alkyl.

It should be appreciated that the compounds of formula (I) may have chiral carbon atoms and therefore may exist as enantiomers. The present invention extends to each enantiomer and to mixtures thereof including racemates.

Preferably where P is -CH=CH- or Q is CR^{1a}=CH the compound exists as the E isomer.

A suitable group of compounds of formula (I) have:

R^1 as hydrogen, fluoro, methyl, ethyl or propyl;

R^2 as hydrogen or one or more of methyl, ethyl, *n*-butyl, phenyl, *iso*-propyl, *t*-butyl, methoxy, ethoxy, n-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amino, acetylamino, methylthio, oxazolo, methylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl;

R^3 as hydrogen, methyl, ethyl, propyl, benzyl, *t*-butyloxycarbonyl or trifluoroacetyl.

Suitable linked R^2 groups include -CH=CH-NH-.

Suitable linked R^1 and R^2 groups are ethylene, propylene, 1,1-dimethylethylene when Q is $-NR^1$; or suitable linked R^1 and R^2 groups are ethylene, propylene, 1,1-dimethylethylene when Q is $-NR^1CH_2$.

In a particular group of compounds of formula (I),

R^1 is hydrogen, fluoro or methyl;

R^2 is hydrogen or one or more of methyl, ethyl, *t*-butyl, methoxy, methoxycarbonyl, methylcarbonyl, ethylcarbonyl, methylamido, acetylamino, methylsulfonyl, oxazole, trifluoromethyl, cyano, chloro, fluoro, or nitro;

R^3 is hydrogen, methyl, ethyl, *n*-propyl, benzyl or *t*-butyloxycarbonyl.

Examples of compounds of one aspect of formula (I) are:

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-nitrocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-trifluoromethylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cinnamide hydrochloride;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-α-methylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxycinnamide;
E-N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-3-yl)-3-phenylacrylamide;
E-3-Furan-2-yl-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-thiophen-2-ylacrylamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2, 4-dichlorocinnamide;
Z-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxycinnamide;
E-3-Indolin-5-yl-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide;
E-3-(1-Methyl-Indolin-2-yl)-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methylsulphonylcinnamide;
E-N-methyl-3-[2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ylcarbamoyl)vinyl] benzamide;
E-3-(Indazolin-3-yl)-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-nitrocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-trifluoromethylcinnamide;

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-ethoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-4-fluorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-6-fluorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-cinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-acetylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-bromocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2-methoxycinnamide;
E-2-Cyano-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)cinnamide;
N-(8-Chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
N-(8-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
N-(8-Chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
N-(8-Bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl-α-fluorocinnamide;
E-N-(8-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Bromo-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(2,4,4-Trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylcinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-6-fluorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-trifluoromethylcinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-4-fluorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(1,1,2-Trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(1,2,4,4-Tetramethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-ethoxycinnamide;

E-N-(8-Chloro-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxycinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-cyanocinnamide;
E-N-(8-Methyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-acetylcinnamide;
E-N-(8-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-cyanocinnamide;
E-N-(8-Chloro-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(5,6,7,8-Tetrahydro-6-methyl[1,6]naphthyridin-3-yl)-cinnamide, and;
E-N-(5,6,7,8-Tetrahydro-6,8,8-trimethyl[1,6]naphthyridin-3-yl)-2-chlorocinnamide.

Examples of compounds of another aspect of formula (I) are:
E-N-(4-Methoxyphenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-n-propyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Cyanophenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Cyanophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(2-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(2-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Methyl-N-benzyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Nitrophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Methyl-N-phenyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Carbomethoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;

E-N-Methyl-3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acryloylamino]benzamide;
E-N-(3-N-Methylsulphonylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide;
E-N-(1,3-Oxazol-5-ylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Acetylaminophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide;
E-N-(3-Ethylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-tert-Butylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Fluorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Carbomethoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide;
E-N-(4-Cyanophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Nitrophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Methoxy-5-trifluoromethylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-1-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone;
E-1-(3,4-Dihydro-2H- quinolin-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone;
E-1-(3,3-Dimethyl-2,3-dihydroindol-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone, and;
E-1-(2,3-Dihydroindol-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone.

When synthesised, these compounds may be isolated in salt form, such as the hydrochloride or trifluoroacetate, and such salts also form part of this invention. Such salts may be used in preparing pharmaceutically acceptable salts. The compounds and their salts may be obtained as solvates, such as hydrates, and these also form part of this invention.

The above compounds and pharmaceutically acceptable salts thereof, especially the hydrochloride, and pharmaceutically acceptable solvates, especially hydrates, form a preferred aspect of the present invention.

The administration of such compounds to a mammal may be by way of oral, parenteral, sub-lingual, nasal, rectal or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral, including sub-lingual, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colorants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art. Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin,

hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents. Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

Accordingly, the present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral

sclerosis (ALS) which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

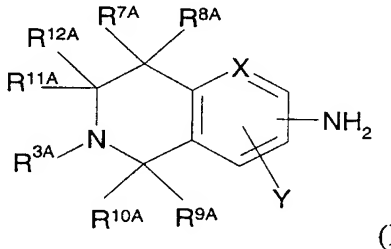
The present invention also provides a method of treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

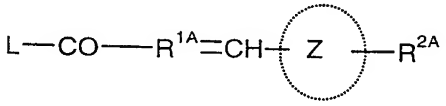
The present invention also provides a process for the preparation of compounds of formula (I), which comprises

(a). for compounds of formula (I) in which P is -NH- and Q is -CR^1=CH-, reacting a compound of formula (II)



(II)

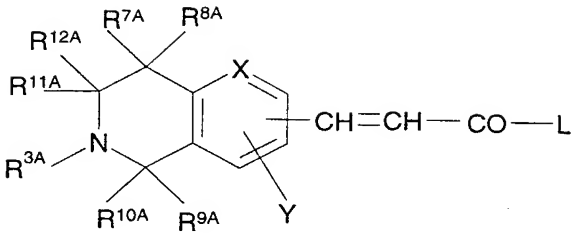
with a compound of formula (III)



(III)

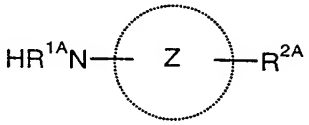
or,

(b) for compounds of formula (I) in which P is -CH=CH- and Q is -NR^1-, reacting a compound of formula (IV)



(IV)

with a compound of formula (V)



(V)

where R^{1A}, R^{2A}, R^{3A}, R^{7A}, R^{8A}, R^{9A}, and R^{10A} are independently R^1, R^2, R^3, R^7, R^8, R^9, and R^{10} as defined for formula (I) or a group or groups convertible thereto; Z, X and Y are as defined for formula (I); and L is OH or a halogen;

and where required converting an R^{1A}, R^{2A}, R^{3A}, R^{7A}, R^{8A}, R^{9A}, or R^{10A} group to an R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group;

converting one R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group to another R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group;

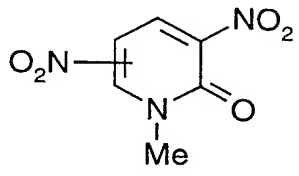
converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

Conventional conditions for condensation of amines with carboxylic acids or active derivatives thereof, such as acid chlorides, may be used. For example the amides and acids may be reacted in the presence of a mixture of ethyl(dimethylaminopropyl)-carbodiimide/hydroxybenzotriazole in a suitable solvent such as dimethyl formamide, and amines and acid chlorides may be reacted together in a suitable solvent such as ethyl acetate or tetrahydrofuran. Alternatively the acid may be treated in solution with oxalyl chloride and then reacted with the amine or its hydrochloride.

Reaction of a compound of formula (III) or (V) which is an acid chloride (L=Cl) in the absence of a base such as triethylamine will lead to formation of the hydrochloride salt of the compound of formula (I). In the presence of a base such as triethylamine the free base will be prepared. Hydrochloride salts can also be obtained by passing HCl gas into a solution of the free base, or adding a solution of HCl in ether.

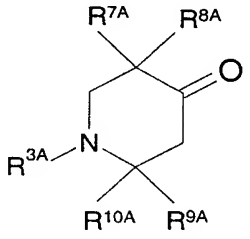
Conversions of an R^{1A}, R^{2A}, R^{3A}, R^{7A}, R^{8A}, R^{9A}, or R^{10A} group to an R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group to another typically arises when one compound of formula (I) is used as the precursor of another compound of formula (I) or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

Compounds of formula (II) in which X is N (i.e.tetrahydronaphthyridines) may be prepared starting from a dinitro-1-methyl-2-pyridone compound of formula (VI)



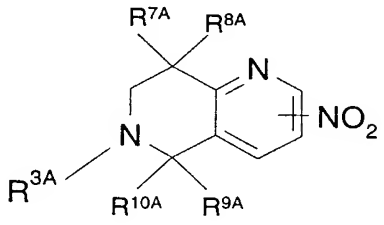
(VI)

by reaction with a 4-piperidone compound of formula (VII)



(VII)

in a solution of ammonia in a suitable solvent such as methanol, to obtain a compound of formula (VIII) using a procedure similar to that of S Takada *et al*, J Med Chem, 1996, **39,** 2844.

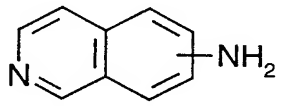


(VIII)

Compounds of formula (VIII) may be converted to compounds of formula (II) wherein X is nitrogen and Y is hydrogen by hydrogenation or reduction of the nitro group. For example, a compound of formula (VIII) may be hydrogenated by treatment with hydrogen in a suitable solvent such as methanol in the presence of a palladium/carbon catalyst. Alternatively, a compound of formula (VIII) may be reduced with stannous chloride in concentrated hydrochloric acid in a suitable solvent such as ethanol.

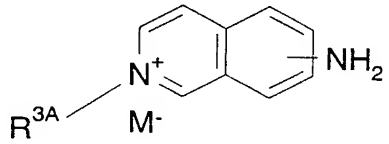
Compounds of formula (VI) may be prepared using the procedure of E. Matsumura, M. Ariga and Y. Tohda, Bull. Chem. Soc. Japan, **52** (8), 2413-2419 (1979).

Compounds of formula (II) in which X is CH and R^{3A}, R^{7A}, R^{8A}, R^{9A}, and R^{10A} are hydrogen (i.e. tetrahydroisoquinolines) may be prepared from the corresponding unsaturated compound of formula (IX)



(IX)

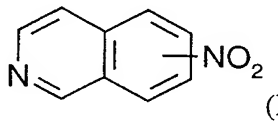
by reaction with a compound $R^{3A}M$ where M is a leaving group such as halogen, especially iodo, or tosylate to obtain an intermediate of formula (X)



(X)

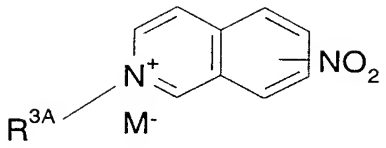
which can be reduced, for example using sodium borohydride, to the compound of formula (II) wherein R^{7A}, R^{8A}, R^{9A}, and R^{10A} are hydrogen. Alternatively the compound of formula (X) can be hydrogenated, for example using hydrogen at 50psi in a solution of acetic/sulphuric acid with a platinum oxide catalyst.

Another route is from a precursor of formula (XI)



(XI)

which can be reacted with $R^{3A}M$, preferably as a tosylate, to obtain the intermediate of formula (XII)



(XII)

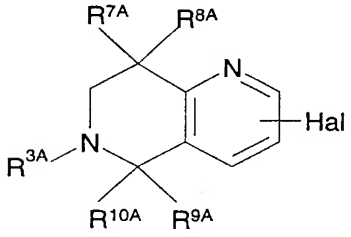
which can then be hydrogenated under the conditions previously described to prepare the compound of formula (II) wherein X is CH and R^{7A}, R^{8A}, R^{9A}, and R^{10A} are hydrogen.

Compounds of formulae (IX) and (XI) and the reagents used are commercially available, or can be prepared from commercially available materials using conventional procedures described in the literature.

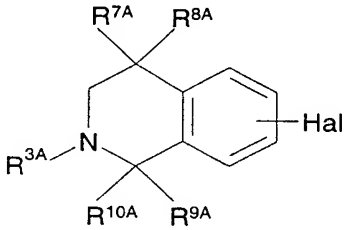
Alternatively, a compound of formula (II) wherein R^{7A}, R^{8A}, R^{9A}, and R^{10A} are hydrogen may be prepared directly from the corresponding nitro compound by catalytic hydrogenation. More specifically 7-amino-tetrahydroisoquinolines may be prepared by the procedure of G E Stokker, Tet. Lett. 1996, 37, 5453.

When R^{3A} is hydrogen, the compound of formula (II) wherein R^{7A}, R^{8A}, R^{9A}, or R^{10A} are hydrogen can be obtained by direct hydrogenation of the compounds of formula (IX) or (XI), using the reagents already described. The NH group may be protected conventionally, for example by making R^{3A} *t*-butoxycarbonyl prior to coupling and then deprotecting R^{3A} under standard conditions, for example using trifluoroacetic acid/methylene chloride.

Compounds of Formula (IV) may be prepared by initially reacting a compound of formula (XII) or formula (XIII)



(XII)



(XIII)

where Hal is a halogen, especially bromine, with an acrylate ester such as ethyl acrylate in conventional conditions. For example the reactants may be heated in the presence of palladium acetate and triethylamine in a suitable solvent such as acetonitrile. This reaction produces the corresponding ester of the L = OH

compound of formula (IV). Deesterification, for example by treatment with sodium or potassium hydroxide, gives the acid (L = OH) of formula (IV). The acid of formula (IV) can be reacted with the amine of formula (V) under conditions mentioned above for reaction of formulae (II) and (III), or converted to the acid chloride, for example by treatment with carbonyl chloride, and then reacted with the amine.

In the reaction of formulae (IV) and (V), the group R^{3A} may be a desired substituent or a protecting group such as carboxylic acid *tert*-butyl ester. The protecting group may be removed at the end of the coupling to provide a compound in which R^3 is H, or to provide a site for introduction of other R^3 groups.

The halo compound (XIII) can be prepared by conventional means from commercial starting materials.

Compounds of formula (XII) are novel and form a further aspect of the present invention.

The aromatic amine compounds of formula (V), typically substituted phenylamines or bicyclic heterocycles such as tetrahydro(iso)quinolines and dihydroindolines, and the cinnamic acid derivatives of formula (III) are also commercially available or obtainable by conventional manipulation of substituents on aromatic acids and amines that are commercially available.

The above described procedures have been based on compounds in which Y is H. Compounds in which Y is a halogen may be prepared by reacting a compound of formula (II), or one of the above described precursors thereof (having an R^{3A} acting protecting group or an R^3 substituent other than hydrogen) with a N-halo-succinimide in a suitable solvent such as acetonitrile, or N-chloromorpholine in a suitable solvent such as acetic acid for compounds where Y is chloro.

When R^{3A} is a protecting group then desired R^3 substuents can be introduced into compounds of formula (II) or (IV) by removal of the protecting group followed by conventional N-substitutions, such as reaction with an appropriate aldehyde in the presence of a suitable reducing agent such as sodium borohydride.

Interconversions where Y is halogen, especially bromo or iodo, into intermediates of formula (II) where Y is alkyl can be carried out using a tetraalkyltin reagent in the presence of a suitable catalyst such as *bis* (triphenylphosphine) Pd (II) dichloride in a suitable solvent such as dimethylformamide at elevated temperature, optionally under argon. Alternatively, compounds of formula (I) where the R^2 substituent is other than halogen and Y is bromo or iodo can also be converted into compounds of formula

(I) where Y is alkyl using an appropriate tetraalkyltin reagent. Other procedures for the interconversion of Y = halogen into Y = alkyl can be found in J. K. Stille, J. Org. Chem., 1990, 55, 3019.

Methods for the preparations of intermediates to other compounds of formula (II) where R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, are alkyl can be found in WO98/41507; T.G.N.Watson., J. Org. Chem., 1998, 63, 406 [for R^{11}, R^{12}, as alkyl] and H. Takechi *et al.*, Synthesis 1992, 778 [for R^7, R^8, as alkyl].

The preparation of compounds of formulae (II) and (IV) is illustrated by the following Descriptions; the preparation of compounds of this invention is illustrated by the following Examples. The utility of compounds of this invention is shown by the Pharmacological Data that follow the Examples. In the Descriptions and Examples, previously made compounds are referred to as, for example, "D1c" - meaning a compound made by Description 1c - and "E19rc" - a compound made as in Example 19rc)

Description 1c

N-2-(4-Nitrophenyl)ethyl-trifluoroacetamide

A solution of trifluoroacetic anhydride (10.6ml) in dichloromethane (100ml) was added dropwise to a stirred solution of 2,6- lutidine (17.44ml) and 4-nitrophenethylamine hydrochloride (15.2g; 75 mmol) at 0°C. The mixture was stirred at 25°C overnight under argon and then washed with dilute citric acid (x2), brine and dried over Na_2SO_4. The material in the organic phase gave the title compound as a pale yellow solid (19.04g).

Description 2c

7-Nitro-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline

The nitro compound **D1c** (2.26g; 9.15 mmol) and paraformaldehyde (0.45g; 14.4 mmol) in acetic acid (10ml) and conc. H_2SO_4 (15ml) were stirred at 25°C for 20h according to the procedure of G.E. Stokker., Tet. Lett., 1996, **37**, 5453. Work up afforded the title compound as a white solid (2.17g).

^1H NMR ($CDCl_3$) δ: 3.10 (2H, m), 3.92 (2H, m), 4.85 + 4.92 (2H, 2xs), 7.38 (1H, t), 8.10 (2H, m); $^m/_z$ (EI): 274 (M^+)

Description 3c

7-Nitro-1,2,3,4-tetrahydroisoquinoline

The trifluoroacetamide **D2c** (17.22g; 63 mmol) was hydrolysed at room temperature using a solution of potassium carbonate (46.6g) in 10% aqueous methanol (660ml). Work-up with dichloromethane gave the title compound (11g).

Description 4c

2-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline

The amine **D3c** (2.08g; 11.7 mmol) was treated with 88% formic acid (3.45ml) and 37% aqueous formaldehyde (5.88ml) at 80°C for 2h according to the procedure of G.M. Carrera and D.S. Garvey, J. Het. Chem., 1992, **29**, 847. Basification with 10% NaOH followed by work-up with ethyl acetate afforded an orange gum(2.3g). Chromatography on Kiesegel 60 in 0-3% methanol - ethyl acetate gave the title compound as an orange solid (1.7g).

MS $^{m}/_{z}$ (CI): 193 (MH^+).

Description 5c

7-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline

The 7-nitro compound **D4c** (0.25g; 1.3 mmol) in methanol (40ml) was hydrogenated over 10% palladium on carbon (100mg) at atmospheric pressure overnight. The catalyst was removed by filtration through a pad of Kieselguhr and evaporation *in vacuo* gave the title compound as a white solid (213mg).

MS $^{m}/_{z}$ (CI): 163 (MH^+)

Description 6c

7-Amino-2-(*t*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared from the compound of **D3c** using di *t*-butyl dicarbonate in 10% aqueous hydroxide in dioxan at 25°C followed by catalytic hydrogenation according to the procedure of Description 5c.

Description 7c

7-Amino-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline

The 7-nitro compound **D2c** (0.99g; 3.6 mmol) in ethanol (50ml) was hydrogenated over 10% palladium on carbon (450mg) at atmospheric pressure for 4h. The catalyst was removed by filtration through a pad of Celite and evaporation *in vacuo* gave the title compound as a white solid (840mg).

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.84 (2H, t), 3.23 (2H, br s), 3.82 (2H, m), 4.66 (2H,d, restricted rotation around C-1), 6.47 (1H, m), 6.57 (1H,m), 6.96 (1H, m)

Description 8c

6-Methyl-3-nitro-5,6,7,8-tetrahydro[1,6[naphthyridine

3,5-Dinitro-1-methyl-2-pyridone (5.97g; 30 mmol) was treated with 1.22M ammonia in methanol (300ml) followed by 1-methyl-4-piperidone (3.73g, 33

mmol) and the mixture heated at 60° for 5h, then allowed to stand at ambient temp for 72h. Evaporated to dryness under reduced pressure and the orange/red residue triturated under a mixture of dichloromethane and diethyl ether, collected by filtration, washed with diethyl ether and dried in air. Chromatography through silica gel, eluting with ethyl acetate, gave the title compound as a red solid (3.4g, 59%); ν_{max} (CH_2Cl_2) 1530 and 1351cm^{-1}

^1H NMR (250MHz, $CDCl_3$) δ: 2.53 (3H, s), 2.85 (2H, t, J = 6 Hz), 3.18 (2H, t, J = 6 Hz), 3.69 (2H, s), 8.14 (1H, d, J = 2 Hz), 9.23 (1H, d, J = 2 Hz)

Description 9c

3-Amino-6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine

6-Methyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine (2.72g, 1.41 mmol) was dissolved in methanol (100ml) and treated with 10% palladium on carbon (1.0g). The mixture was hydrogenated for 2h. The catalyst was removed by filtration through Celite, the filter bed washed with methanol and the filtrate evaporated to dryness under reduced pressure to give a yellow solid, which was triturated under diethyl ether and the solids collected by filtration, washed with diethyl ether and dried *in vacuo* (1.89g, 83%)

^1H NMR (250MHz, $CDCl_3$) δ: 2.46 (3H, s), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.50 (2H, s), 3.56 (2H, br s, exchangeable), 6.65 (1H, d, J = 2 Hz), 7.92 (1H, d, J = 2 Hz)

Description 10c

5-Amino-2-methylisoquinolinium iodide

To a solution of 5-aminoisoquinoline (14.4g, 100mmol) in acetone (300ml) was added iodomethane (14.4ml). The solution was briefly stirred and then allowed to stand for 2h. The yellow precipitate was then filtered, washed with acetone and dried to afford the title compound as a yellow solid (18.8g).

Description 11c

5-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline

Sodium borohydride (17.8g, 0.47mol) was added portionwise over 2h to an ice cold solution of 5-amino-2-methylisoquinolinium iodide (18.8g, 65mmol) in methanol (1.5L) and water (60ml). The mixture was then stirred at 25°C for 18h. and concentrated *in vacuo*. The residue was extracted into water and dichloromethane. The organic layer was dried (Na_2SO_4) and concentration *in vacuo* gave the title compound (8.87g).

Description 12c

7-Amino-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline

The 7-nitro compound **D2c** (0.99g; 3.6 mmol) in ethanol (50ml) was hydrogenated over 10% palladium on carbon (450mg) at atmospheric pressure for 4h. The catalyst was removed by filtration through a pad of Celite and evaporation *in vacuo* gave the title compound as a white solid (840mg).

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.84 (2H, t), 3.23 (2H, br s), 3.82 (2H, m), 4.66 (2H,d, restricted rotation around C-1), 6.47 (1H, m), 6.57 (1H,m), 6.96 (1H, m)

Description 13c

7-Amino-8-chloro-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline

To a solution of amine **D12c** (1.00g) in acetonitrile (20ml) N-chlorosuccinimide (0.60g) was added and the solution stirred at room temperature for 6 days. The solution was diluted with ethyl acetate, washed with water and the organic phase dried ($MgSO_4$) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane then 2% methanol/dichloromethane) to give 7-amino-8-chloro-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline as a pale yellow solid (0.72g).

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.85 (2H, m), 3.83 (2H, dt, restricted amide rotation), 4.76 (2H, s), 6.68 (1H, m) and 6.89 (1H, m).

Description 14c

7-Amino-8-bromo-1,2,3,4-tetrahydro-2-trifluoroacetylisoquinoline

The title compound (0.27g) was prepared from amine **D12c** (0.24g) and N-bromosuccinimide (0.20g) according to the method of Description 13c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.85 (2H, m), 3.76 - 3.87 (2H, m, restricted amide rotation), 4.72 (2H, d due to restricted amide rotation), 6.68 (1H, m) and 6.93 (1H, m).

Description 15c

5-Iodo-7-nitro-1,2,3,4-tetrahydroisoquinoline

The nitro compound **D3c** (750mg; 3.9mmol) and N-iodosuccinimide (1.13g) in triflic acid (5ml) was stirred at 25°C overnight. The mixture was poured cautiously into saturated $NaHCO_3$ and then extracted into ether (2x). The combined organic extracts were washed with aqueous sodium thiosulfate, dried ($MgSO_4$) and evaporation *in vacuo* gave a residue. Chromatography on Kieselgel 60 in 2% methanol - dichloromethane gave the title compound (650mg).

Description 16c

5-Iodo-7-nitro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared from **D15c** and trifluoroacetic anhydride using a procedure similar to that of Description 6.
MS m/z (API$^+$): 401 (MH^+; 45%).

Description 17
5-Chloro-7-nitro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline
D16c (810mg) in dry DMF (15ml) was treated with copper (I) chloride (605mg) and heated at 125°C under argon for 18h. After cooling, the mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with water (x 3), aqueous sodium thiosulfate, brine and dried ($MgSO_4$). Evaporation *in vacuo* gave the title compound as a red gum (519mg).
^1H NMR ($CDCl_3$) δ: 3.09 (2H, m), 3.96 (2H, m), 4.85, 4.92 (2H, 2s, rotamers), 7.99 (1H, m), 8.20 (1H, m).

Description 18c
7-Amino-5-chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline
A solution of the nitro compound **D17c** (2.14mmol) in ethanol (20ml) at 50°C was treated with a solution of tin (II) chloride (1.42g) in c. HCl (3ml). The resultant yellow solution was basified with 10% aqueous sodium hydroxide and the product extracted into dichloromethane. Flash chromatography on Kieselgel 60 (5% methanol - dichloromethane) gave the title compound.
^1H NMR ($CDCl_3$) δ: 2.84 (2H, m), 3.67 (2H, brs), 3.83 (2H, m), 4.61, 4.67 (2H, 2s, rotamers), 6.33 (1H, m), 6.65 (1H, m).

Description 19c
7-Amino-5-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline
The title compound was prepared from **D16c** and copper (II) bromide using a method similar to that of Description 10 followed by tin (II) chloride reduction according to the procedure used in Description 18.
^1H NMR ($CDCl_3$) δ: 2.86 (2H, m), 3.68 (2H, brs), 3.85 (2H, m), 4.62, 4.69 (2H, 2s, rotamers), 6.39 (1H, m), 6.85 (1H, m).

Description 20c
7-Nitro-2,4,4-trimethyl-4H-isoquinoline-1,3-dione
2,4,4-Trimethyl-4H-isoquinoline-1,3-dione (5g, 24.6mmol) [prepared according to H. Takechi *et al.*, Synthesis. 1992, 778] in concentrated sulfuric acid (50ml) at 0°C was treated with fuming nitric acid (2.5ml, dropwise) over 5 min and the

reaction warmed to 25°C. After stirring for 30 min at 25°C the reaction mixture was poured into ice water (100ml) and the organics extracted into dichloromethane (3x50ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound (5.31g, 86%).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.70 (6H, s), 3.42 (3H, s), 7.69 (1H, d, J = 9 Hz), 8.46 (1H, dd, J = 9, 2 Hz), 9.07 (1H, d, J = 2 Hz); $^m/_z$ (API$^+$): 249 $(M+H)^+$

Description 21c

7-Amino-2,4,4,-trimethyl-4H-isoquinoline-1,3-dione

7-Nitro-2,4,4-trimethyl-4H-isoquinoline-1,3-dione (45g, 20mmol) was dissolved in a methanol (500ml)/dichloromethane (100ml) mixture and treated with 10% Pd/C (0.5g). The reaction mixture was hydrogenated for 2h before removal of the palladium catalyst by filtration through Celite. The filtrate was evaporated to dryness *in vacuo* to give the title compound (4.4g, quant).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.58 (6H, s), 3.36 (3H, s), 3.83 (2H, brs), 6.95 (1H, dd,J = 6, 3 Hz), 7.24 (1H, d, J = 6 Hz), 7.48 (1H, d, J = 3 Hz); MS $^m/_z$ (API$^+$): 219 $(M+H)^+$

Description 22c

7-Amino-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline, hydrochloride

7-Amino-2,4,4-trimethyl-4H-isoquinoline-1,3-dione (4g, 18.3mmol) was dissolved in tetrahydrofuran (400ml) and heated at reflux (~61°C). Borane-tetrahydrofuran complex (88ml, 1M solution in THF) was added dropwise to the mixture and heating continued for a further 3 h. The cooled reaction (0°C) was treated with methanol (400ml) dropwise to destroy residual borane, followed by evaporation *in vacuo*. The resultant residue was heated at reflux in 3N HCl (400ml) for 30 min. The mixture was cooled to 0°C and treated with NaOH pellets until basic (pH 9). The free amine was extracted into dichloromethane (4x100ml) before drying over magnesium sulfate and evaporation *in vacuo*. The resulting light brown oil was dissolved in dichloromethane (50ml) and treated with hydrogen chloride (1M solution in ether) until acidic (pH 2). Solvent removal *in vacuo* followed by trituration with ether yielded the title compound as an off-white powder (3.3g, 79%).

^{1}H NMR (free base 250 MHz, $CDCl_3$) δ: 1.25 (6H, s), 2.37 (2H, s), 2.39 (3H, s), 3.43 (2H, s), 3.51 (2H, brs), 6.32 (1H, d, J = 2 Hz), 6.54 (1H, dd, J = 8, 2 Hz), 7.09 (1H, d, J = 8 Hz); $^m/_z$ (API$^+$): 191 $(M+H)^+$

Description 23c

3,4-Dihydro-3,3-dimethyl-7-nitroisoquinoline

To a stirred solution of potassium nitrate (2.53g) in sulfuric acid (14ml) at 0°C was added dropwise a solution of 3,4-dihydro-3,3-dimethyl isoquinoline (3.68g; 23mmol) [prepared according to the procedure of T.J.N.Watson, *J. Org. Chem.*, 1998, 63, 406] in sulfuric acid (13.5ml). The resultant solution was stirred at room temperature for 1.5h and then heated to 60°C for 4.5h. The solution was then cooled to room temperature, and poured on to ice.; 0.880 ammonia was added until the solution was neutral, and the product was extracted into dichloromethane (x3). The combined organic phases were, dried over magnesium sulphate, and then evaporated *in vacuo* to afford the title compound (4.22g).
^{1}H NMR ($CDCl_3$) δ: 1.27 (6H, s), 2.85 (2H, s), 7.34 (1H, d, J = 8 Hz), 8.17 (1H, d, J = 2 Hz), 8.23 (1H, dd, J = 8, 2 Hz), 8.33 (1H, s).

Description 24c
3,3-Dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline
Sodium borohydride (1.57g; 41.38mmol) was added portionwise to a solution of 3,4-dihydro-3,3-dimethyl-7-nitroisoquinoline (4.22g; 20.69mmol) in methanol (150ml). The resultant solution was stirred at room temperature for 2 h. The methanol was evaporated *in vacuo* and the residue partitioned between water and dichloromethane. The organic layer was dried (Na_2SO_4) and then evaporated *in vacuo* to afford the title compound (3.81g).
^{1}H NMR ($CDCl_3$) δ: 1.20 (6H, s), 1.40 - 1.53 (1H, brs), 2.72 (2H, s), 4.14 (2H, s), 7.20 (1H, d, J = 8 Hz), 7.37 (1H, s), 7.98 (1H, dd, J = 8, 2 Hz).

Description 25c
3,3-Dimethyl-7-nitro-1,2,3,4-tetrahydro-2-trifluoroacetylisoquinoline
A solution of 2,6-lutidine (2.29ml; 19.69mmol) and 3,3-dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (3.7g; 17.9mmol) in dichloromethane (150ml) was treated dropwise, with ice cooling, trifluoroacetic anhydride (2.53ml, 17.9mmol) in dichloromethane (50ml). The reaction was then allowed to warm to 25°C and stirred for 18h. The resultant mixture was washed with 5M HCl, brine, dried (Na_2SO_4) and then evaporated *in vacuo* to afford the title compound (5.82g).
^{1}H NMR ($CDCl_3$) δ: 1.51 (6H, s), 2.97 (2H, s), 4.61 (2H, s), 7.43 (1H, d, J = 8 Hz), 8.12 (1H, d, J = 2 Hz), 8.24 (1H, dd, J = 8, 2 Hz).

Description 26c
7-Nitro-2,3,3-trimethyl-3,4-dihydroisoquinolinium iodide
D24c (1.0g, 4.9mmol) was dissolved in acetone (100ml) and treated with iodomethane (1ml, 16mmol). The reaction was stirred at room temperature for

18h. The resultant precipitate was collected by filtration and dried; pale yellow powder (1.5g, 88%).
MS m/z (API$^+$): 219 $(M)^+$

Description 27c
7-Nitro-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinoline
D26c (200mg, 5.8mmol) was reduced with sodium borohydride (300mg); 7.9mmol) in a manner similar to that of Description 24c. Purification by chromatography eluting with a dichloromethane solution of ammonia in methanol (0.5% conc. NH_3: 4.5% MeOH: 95% CH_2Cl_2) gave the title compound as a pale yellow oil (93mg, 73%).
^{1}H NMR ($CDCl_3$) δ: 1.10 (6H, s), 2.40 (3H, s), 2.78 (2H, s), 3.80 (2H, s), 7.21 (1H, d, J = 8 Hz), 7.90 (2H, m).

Description 28c
7-Amino-2,3,3,-trimethyl-1,2,3,4-tetrahydroisoquinoline
The title compound was prepared from **D27c** using a method similar to that of Description 2c. For ease of handling the compound was converted into a monohydrochloride.
^{1}H NMR ($CDCl_3$) δ: 1.07 (6H, s), 2.35 (3H, s), 2.59 (2H, s), 3.46 (2H, brs), 3.64 (2H, s), 6.37 (1H, d, J = 2 Hz), 6.50 (1H, dd, J = 8, 2 Hz), 6.84 (1H, d, J = 8 Hz).

Description 29c
7-Amino-8-chloro-2,3,3,-trimethyl-1,2,3,4-tetrahydroisoquinoline
Chlorination of **D28c** (900mg; 4.74 mmol) with N-chloromorpholine (600mg; 4.90 mmol) in glacial acetic acid (30ml) for 30 min at 25°C followed by basic work-up with dichloromethane gave the title compound (700mg).
^{1}H NMR ($CDCl_3$) δ: 1.06 (6H, s), 2.40 (3H, s), 2.60 (2H, s), 3.67 (2H, s), 3.92, (2H, brs), 6.62 (1H, d, J = 8 Hz), 6.79 (1H, d, J = 8 Hz); m/z (API$^+$): 225.1 (MH^+; 100% expected isotope pattern)

Description 30c
7-Amino-8-bromo-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline
To a solution of 7-amino-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline from **D22c** (7g) in acetonitrile (200ml), was added N-bromo succinimide (7.21g) portionwise over 10 min. The reaction mixture was cooled in an ice/methanol bath to prevent any large exotherm and then stirred under argon for 45 min. The reaction was allowed to warm to room temperature, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with

brine, dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford a brown solid which was purified using dry flash column chromatography eluting with ethyl acetate. Combination of appropriate fractions afforded the title compound as an orange gum (3.95g).

^1H NMR ($CDCl_3$) δ: 1.26 (6H, s), 2.33 (2H, s), 2.45 (3H, s), 3.49 (2H, s), 4.00 (2H, s), 6.67 (1H, d), 7.08 (1H, d).

Description 31c

7-Amino-8-ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline

A solution of **D30c** (3.95g) and lithium chloride (1.87g) in dry dimethylformamide (120ml) was treated with tetraethyl tin (5.81ml) followed by a catalytic amount of *bis* (triphenylphosphine) palladium (II) dichloride (350mg). The reaction mixture was then stirred under argon at 120°C overnight. After cooling, the solvent was removed *in vacuo* and the residual oil was dissolved in dichloromethane and filtered through Celite, washing with dichloromethane. The organic phase was evaporated *in vacuo* to afford a dark orange oil which was purified using dry flash column chromatography eluting with ethyl acetate. Combination of appropriate fractions gave the title compound as a yellow gum (1.6g).

^1H NMR ($CDCl_3$) δ: 1.14 (3H, t), 1.27 (6H, d), 2.33 (2H, s), 2.47 (5H, m), 3.51 (2H, s), 6.60 (1H, d), 7.02 (1H, d).

Description 32c

1,2-Dimethyl-3,4-dihydroisoquinolinium iodide

1-Methyl-3,4-dihydroisoquinoline (780mg) was dissolved in acetone (7ml) and iodomethane (0.38ml) added. The solution was allowed to stand overnight at room temperature. The product was obtained as pale yellow crystals (1.4g).

^1H NMR (250MHz, d_6DMSO) δ: 2.66 (3H, s), 2.99 (2H, t, J = 7.5 Hz), 3.56 (3H, s), 3.88 (2H, t, J = 7.5 Hz), 7.36 (2H, m), 7.60 (1H, t, J = 7.5 Hz), 7.94 (1H, d, J = 7.5 Hz).

Description 33c

1,1,2-Trimethyl-1,2,3,4-tetrahydroisoquinoline

Methyl magnesium bromide (4.5ml, 3M in Et_2O) was added to a stirred suspension of 1,2-dimethyl-3,4-dihydroisoquinolinium iodide (1.3g) in dry THF (20ml) at -70°C under argon. After 1h, the mixture was allowed to warm slowly to room temperature and stirred overnight. The mixture was quenched by cautious addition of water and extracted with ethyl acetate. The extract was washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound as a pink oil (730mg).

^{1}H NMR (250MHz, $CDCl_3$) δ: 1.40 (6H, s), 2.44 (3H, s), 2.87 (4H, s), 7.15 (4H, m).

Description 34c

1,1,2-Trimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline

The amine **D33c** (620mg) was converted into the sulfate salt and added to an ice-cooled solution of potassium nitrate (420mg) in conc. H_2SO_4 (5ml). When the addition was complete the ice bath was removed and the mixture stirred overnight at room temperature. The mixture was poured onto ice, made basic with conc. aq. ammonia and extraction with dichloromethane yielded an oil which was purified by chromatography eluting with dichloromethane: methanol: ammonia. The product was obtained as a red oil (430mg) [predominantly the desired 7-nitro derivative].

^{1}H NMR (250MHz, $CDCl_3$) δ: 1.45 (6H, s), 2.45 (3H, s), 2.92 (4H, m), 7.20 (1H, d, J = 8 Hz),7.95 (1H, dd, J = 8, 2 Hz), 8.15 (1H, d, J = 2 Hz).

Description 35c

7-Amino-3,4-dihydroisoquinoline

7-Nitro-3,4-dihydroisoquinoline (0.60g, 3.4mmol) [prepared according to the procedure of A.P. Venkov *et al*, Syn. Commun., 1996 **26** 127] was dissolved in ethanol (100ml) and heated to 60°C. This hot solution was treated with a solution of tin (II) chloride dihydrate (3.08g, 13.7mmol) in conc. HCl (10ml). The resultant mixture was heated at 60° for 1h. Upon cooling, the reaction mixture was poured into water (100ml) and basified (pH 9) with KOH pellets, liberating an oily residue. This residue was extracted into dichloromethane and dried over magnesium sulfate. Purification by chromatography through silica gel, eluting with (0.5% conc. ammonia : 4.5% methanol : 95% dichloromethane) yielded the title compound as a dark yellow oil (0.44g, 88%).

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.63 (2H, t, J = 7 Hz), 3.67 (2H, brs), 3.73 (2H, m, J = 7, 2 Hz), 6.62 (1H, d, J = 2 Hz), 6.70 (1H, dd, J = 8, 2 Hz), 6.95 (1H, d, J = 8 Hz), 8.24 (1H, s).

Description 36c

7-Amino-2-methyl-3,4-dihydroisoquinolinium iodide

7-Amino-3,4-dihydroisoquinoline (0.40g, 2.74mmol) in acetone (125ml) was treated with iodomethane (0.50ml, 8.03mmol) and left stirring at room temperature for 18 h. The resultant yellow precipitate was collected by filtration and dried *in vacuo* at ambient temperature (0.73g, 92%).

MS $^m/_z$ (API$^+$): 161 $(M)^+$

Description 37c

(±) 7-Amino-1,2-dimethyl-tetrahydroisoquinoline

(±) 7-Amino-2-methyl-3,4-dihydroisoquinolinium iodide (0.50g, 1.7mmol) was suspended in anhydrous tetrahydrofuran (50ml) and cooled to -78°C. The cooled solution was treated with methyl magnesium chloride (2.14ml of a 3M solution in THF, 6.96mmol), added as a single portion. The reaction was allowed to reach room temperature over 18 h before being poured into water (50ml). The organic solvent was removed *in vacuo* and the organic product extracted into dichloromethane. Drying over magnesium sulfate and evaporation *in vacuo* furnished the title compound as a pale yellow oil (0.3g, 98%). For ease of handling the product was converted into a monohydrochloride.

^{1}H NMR (250MHz, $CDCl_3$) δ: 1.37 (3H, d, J = 7 Hz), 2.46 (3H, s), 2.54 - 2.83 (3H, m), 3.00 (1H, m), 3.50 (3H, m), 6.45 (1H, d, J = 2 Hz), 6.51 (1H, dd, J = 8, 2 Hz), 6.88 (1H, d, J = 8 Hz).

Description 38c

4,4-Dimethyl-7-nitro-3,4-dihydroisoquinoline

The title compound was prepared in a manner to that descibed in Description 35c.

MS m/z (API$^+$): 205 (MH^+; 100%).

Description 39c

2,4,4-Trimethyl-7-nitro-3,4-dihydroisoquinolinium iodide.

The title compound was prepared in a manner to that descibed in Description 36c.

MS m/z (API$^+$): 219 (MH^+; 100%).

Description 40c

7-Nitro-1,2,4,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline

D39c (1.5g, 4.3mmol) in THF (50ml) was stirred under argon and dimethyl zinc in toluene (3.3ml, 2M solution) added with rapid stirring at 0°C. The mixture was allowed to warm to room temperature over 1h, quenched with satd. ammonium chloride and concentrated *in vacuo*. Work-up with dichloromethane gave the title compound (0.9g, 90%).

MS m/z (API$^+$): 235 (MH^+; 100%).

Description 41c

7-Amino-1,2,4,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline

Prepared from **D40c** in a manner similar to that of Description 2c.

^{1}H NMR ($CDCl_3$) δ: 1.34 (3H, s), 1.35 (3H, s), 1.49 (3H, d, J = 7Hz), 2.55 - 2.66 (1H, m), 2.62 (3H, brs), 2.89 (1H, m), 3.50 (2H, brs), 3.77 - 3.90 (1H, m), 6.47 (1H, d, J = 2 Hz), 6.59 (1H, dd, J = 8, 2 Hz), 7.11 (1H, d, J = 8 Hz).

Description 42c
7-Amino-8-methyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline
A solution of **D30c** and lithium chloride in dry dimethylformamide was treated with tetramethyl tin in a manner similar to that of Description 31c.

Description 43c
7-Amino-8-chloro-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline
The title compound was prepared from **D22c** and N-chloromorpholine using a procedure similar to that of Description 29c.

Description 44c
7-Amino-8-chloro-4,4-dimethyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline
^{1}H NMR (250MHz, $CDCl_3$) δ: 1.27 (6H, s), 3.50, 3.63 (2H, 2s, rotamers), 4.05 (2H, brs), 4.76 (2H, s), 6.73 (1H, m), 7.07 (1H, m).

Description 45c
1,3,3-Trimethylpiperidin-4-one
The title compound was prepared according to the procedure of Katvalyan *et al.*, Bull. Acad. Sci. USSR (Engl) 1968, 2436.
b.p 70 °C at 16mm Hg; $^m/_z$ (API^+): 142.1 (MH+)

Description 46c
3-Nitro-5,6,7,8-tetrahydro-6,8,8-trimethyl[1,6]naphthyridine
3,5-Dinitro-1-methylpyridin-2-one [prepared by the method of E. Matsumura, M. Ariga and Y. Tohda, Bull. Chem. Soc. Japan, 1979, **52**, 2413-2419] (2g; 10mmol) was suspended in MeOH (50ml) and treated with 0.88 aq. ammonia (10ml; 157mmol). 1,3,3-Trimethylpiperidin-4-one (1.7g; 12mmol) was added and the mixture heated at 70°C for 5h. The mixture was cooled to room temperature then evaporated to dryness *in vacuo*. The residue was digested with dichloromethane (2x50ml) and the hot solution decanted from the red gum. The extracts were combined, evaporated to dryness *in vacuo* and the residue purified by chromatography on SiO_2, with 50% ethyl acetate : 60-80 °C petroleum to give the title compound as a yellow oil, which solidified on standing (1.05g; 48%).

^{1}H NMR (250 MHz; $CDCl_3$) δ: 1.38 (6H, s), 2.47 (3H, s), 2.55 (2H, s), 3.64 (2H, s), 8.09 (1H, d, J = 3 Hz), 9.25 (1H, d, J = 3 Hz); $^m/_z$ (API^+): 222.1 (MH+)

Description 47c

3-Amino-5,6,7,8-tetrahydro-6,8,8-trimethyl[1,6]naphthyridine

The product from **D46c** (930mg; 4.20mmol) was dissolved in MeOH (30ml) and the mixture hydrogenated in a manner similar to that of Description 2 to give the title compound (795mg; 84%).

^{1}H NMR (250 MHz; CD_3OD) δ: 1.73 - 1.99 (2H, m), 2.34 - 2.55 (5H, m), 2.63 (1H, d, J = 17 Hz), 3.29 and 3.36 (1H, dd, J = 17, 5 Hz), 3.66 - 3.71 (1H, m), 3.99 (1H, d, J = 6 Hz), 6.95 (1H, d, J = 3 Hz), 7.95 (1H, d, J = 3 Hz).

Example 1c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-nitrocinnamide

3-Nitrocinnamic acid (195mg; 1.0 mmol), ethyldimethylaminopropyl carbodiimide (194mg; 1.3 mmol) and 1-hydroxybenzotriazole (136mg; 1.0 mmol) in dry DMF (12ml) was stirred at room temperature for 30 min. A solution of the N-methyl amine **D5c** (164mg; 1.0 mmol) in dichloromethane (5ml) was added and the mixture kept at room temperature overnight. The resultant cream precipitate was removed by filtration and the residue washed well with ether:hexane. The residue was dried *in vacuo* and gave the title compound as an off white solid (0.5g).

^{1}H NMR (250MHz, d^6 DMSO) δ: 2.35 (2H, br, overlapping), 2.74 (3H, s), 2.90 (2H, br), 4.20 (2H, br), 6.90 (1H, d, J = 16 Hz), 7.07 (1H, d, J = 8Hz), 7.39 (1H, dd), 7.50 (1H, d, J = 16Hz), 7.60 (1H, t), 7.94 (1H, d, J = 8Hz), 8.10 (1H, m), 8.32 (1H, narrow t);

MS $^m/_z$ (API): 338 (MH^+; 100%)

Example 2c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-trifluoromethylcinnamide

3-Trifluoromethylcinnamoyl chloride (234mg; 1.0mmol) was added to a stirred solution of amine **D5c** (162mg; 1.0mmol) in dichloromethane (25ml) containing dry triethylamine (0.3ml). The mixture was kept at room temperature overnight and work-up similar to that for Example 1c, followed by flash chromatography on Kieselgel 60 (10% methanol:ethyl acetate) gave the title compound as a buff powder (200mg; 55%).

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.46 (3H, s), 2.69 (2H, t), 2.89 (2H, t), 3.56 (2H, s), 6.62 (1H, d, J = 16 Hz), 7.08 (1H, d, J = 6.6Hz), 7.30 (1H, m), 7.40 (1H, brs), 7.52 (1H, t), 7.64 (3H, m), 7.75 (1H, d, J = 16 Hz), 7.79 (1H, s); $^m/_z$ (API): 361.2 (MH^+; 100%)

Example 3c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cinnamide hydrochloride

The title compound (0.20g) isolated as a pale yellow solid, was prepared from amine **D5c** (0.16g) and cinnamic acid according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.43 (3H, s), 2.66 (2H, t), 2.87 (2H, t), 3.52 (2H, s), 6.56 (1H, d), 7.05 (1H, d), 7.26 - 7.52 (6H, m), 7.67(1H, br. s.) and 7.73(1H, d);

MS $^m/_z$ (API): 293.2 (MH^+; 100%)

Example 4c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxycinnamide

The title compound (0.28g) isolated as a pale yellow solid, was prepared from amine **D5c** (0.16g) and 2-methoxycinnamic acid (0.18g) according to the procedure of Example 1c

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.63 (2H, t), 2.84 (2H, t), 3.51 (2H, s), 3.80 (3H, s), 6.74 (1H, d), 6.85(2H, m), 6.99(1H, d), 7.20 - 7.43(4H, m), 8.00(1H, d) and 8.12(1H, br. s); $^m/_z$ (API): 323.2 (MH^+; 100%)

Example 5c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chlorocinnamide

The title compound (0.23g) was prepared from amine **D5c** (0.16g) and 4-chlorocinnamic acid (0.18g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.36 (3H, s), 2.60 (2H, t), 2.84 (2H, t), 3.40 (2H, s), 6.62 (1H, d), 6.97 (2H, m), 7.25 (4H, Abq), 7.33 (2H, m), 7.60 (1H, d) and 8.81 (1H, br. s);

MS $^m/_z$ (API): 327, 329 (MH^+)

Example 6c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chlorocinnamide

The title compound (0.14g) was prepared from amine **D5c** (0.16g) and 3-chlorocinnamic acid (0.18g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.62 (2H, t), 2.84 (2H, t), 3.44 (2H, s), 6.62 (1H, d), 7.00 (1H, m), 7.19 - 7.39(6H, m), 7.61 (1H, d) and 8.50 (1H, br. s.);
MS $^m/_z$ (API): 327, 329 (MH^+; 100%)

Example 7c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-methoxycinnamide
The title compound (0.14g) was prepared from amine **D5c** (0.16g) and 3-methoxycinnamic acid (0.18g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.63 (2H, t), 2.83 (2H, t), 3.43 (2H, s), 3.75 (3H, s), 6.63 (1H, d), 6.85 (1H, d), 6.96 - 7.05 (3H, m), 7.18 - 7.33 (3H, m), 7.67 (1H, d) and 8.41 (1H, br. s); $^m/_z$ (API): 323 (MH^+; 100%)

Example 8c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-α-methylcinnamide
The title compound (0.14g) was prepared from amine **D5c** (0.16g) and α-methylcinnamic acid (0.16g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.14 (3H, s), 2.42 (3H, s), 2.65 (2H, t), 2.87 (2H, t), 3.51 (2H, s), 7.03 (1H, d), 7.26 - 7.41(8H, m) and 7.86 (1H, s); MS $^m/_z$ (API): 307 (MH^+; 100%)

Example 9c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide
The title compound (0.17g) was prepared from amine **D5c** (0.16g) and 2-chlorocinnamic acid (0.18g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.31 (3H, s), 2.59 (2H, t), 2.80 (2H, t), 3.40 (2H, s), 6.66 (1H, d), 6.96 (1H, d), 7.09 (1H, t), 7.20 (1H, dt) 7.20 - 7.37 (3H, m), 7.43 (1H, d), 8.09 (1H, d) and 8.83 (1H, br. s.); MS $^m/_z$ (API): 327, 329 (MH^+)

Example 10c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxycinnamide
The title compound (0.18g) was prepared from amine **D5c** (0.16g) and 4-methoxycinnamic acid (0.18g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.34 (3H, s), 2.58 (2H, t), 2.80 (2H, t), 3.37 (2H, s), 3.73 (3H, s), 6.58 (1H, d), 6,72 (2H, d), 6.94 (1H, m), 7.30 (2H, d), 7.39 (2H, br. s.), 7.65 (1H, d) and 9.00(1H, br. s.); $^m/_z$ (API): 323 (MH^+)

Example 11c

E-N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-3-yl)-3-phenylacrylamide

The title compound (0.18g) was prepared from amine **D9c** (0.16g) and cinnamic acid (0.16g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.77 (2H, t), 3.01 (2H, t), 3.57 (2H, s), 6.46 (1H, d), 7.35 (3H, m), 7.47 (2H, m), 7.73 (1H, d), 8.03 (1H, s) 8.25 (1H, br. s) and 8.40 (1H, s); $^m/_z$ (API): 293 (MH^+)

Example 12c

E-3-Furan-2-yl-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

The title compound (0.22g) was prepared from amine **D5c** (0.16g) and 3-furan-2-yl acrylic acid (0.14g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.63 (2H, t), 2.86 (2H, t), 3.42 (2H, s), 6.40 (1H, m), 6.47 (1H, m), 6.54 (1H, d), 6.97 (1H, d), 7.27 - 7.32 (2H, m), 7.41 (1H, s.), 7.48 (1H, d) and 8.48 (1H, br. s.); $^m/_z$ (API): 283 (MH^+; 100%)

Example 13c

E-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-thiophen-2-ylacrylamide

The title compound (0.23g) was prepared from amine **D5c** (0.16g) and 3-thiophen-2-yl acrylic acid (0.15g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.63 (2H, t), 2.83 (2H, t), 3.42 (2H, s), 6.45 (1H, d), 6.98 (2H, m), 7.11 (1H, m), 7.27 - 7.30 (3H, m), 7.81 (1H, d) and 8.55 (1H, br. s.).

MS $^m/_z$ (API): 299 (MH^+; 100%)

Example 14c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2, 4-dichlorocinnamide

The title compound (0.36g) was prepared from amine **D5c** (0.16g) and 2, 4-dichlorocinnamic acid (0.22g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.51 (3H, s), 2.89 - 2.96 (4H, m), 3.85 (2H, s), 7.07 (1H, d), 7.12 (1H, d), 7.49 - 7.56 ((3H, m), 7.70 (2H, m), 7.79 (1H, d) and 10.57 (1H, br. s).

MS $^m/_z$ (API): 361, 363 (MH^+; 100%)

Example 15c

Z-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxycinnamide

The title compound (0.20g) was prepared from amine **D5c** (0.16g) and Z-2-methoxycinnamic acid (0.18g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.42 (3H, s), 2.64 (2H, m), 2.83 (2H, m), 3.49 (2H, s), 3.83 (3H, s), 6.10 (1H, d J = 12Hz), 6.90 - 7.32 (8H, m) and 7.44(1H, d);
MS $^m/_z$ (API): 323 (MH^+; 100%)

Example 16c
E-3-Indolin-5-yl-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide
The title compound (0.14g) was prepared from amine **D5c** (0.16g) and E-3-indolin-5-yl acrylic acid (0.19g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, d^6-DMSO) δ: 2.70 (3H, s), 2.95 (2H, m), 3.16 (2H, m), 4.04 (2H, s), 6.50 (1H, s), 6.75 (1H,d) 7.15 (1H, d), 7.41 - 7.57 (5H, m), 7.65 (1H, d), 7.79 (1H, s), 10.18 (1H, s) and 11.35 (1H, s); $^m/_z$ (API): 332 (MH^+)

Example 17c
E-3-(1-Methyl-Indolin-2-yl)-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide
The title compound (0.20g) was prepared from amine **D5c** (0.16g) and E-3-(1-methyl-indolin-2-yl) acrylic acid (0.20g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.43 (3H, s), 2.66 (2H, t), 2.88 (2H, t), 3.54 (2H, s), 3.77 (3H, s), 6.60 (1H, d), 6.89 (1H, s) 7.05 (2H, m), 7.21 - 7.31 (2H, m), 7.42 (1H, br.s), 7.56 (1H, d), 7.62 (1H, br. s) and 7.86 (1H, d); $^m/_z$ (API): 345 (MH^+; 100%)

Example 18c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)--3-chloro-4-methoxycinnamide
The title compound (0.37g) was prepared from amine **D5c** (0.16g) and E-3-chloro-4-methoxycinnamic acid (0.22g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, d^6-DMSO) δ: 2.87 (3H, s), 3.05 (2H, m), 3.38 (2H, m), 3.91 (3H, s), 4.34 (2H, s), 6.81 (1H, d), 7.21 (2H, m), 7.47 - 7.71 (5H, m) and 10.35 (1H, br. s);
MS $^m/_z$ (API): 357, 359 (MH^+; 100%)

Example 19c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methylsulphonylcinnamide

The title compound (0.17g) was prepared from amine **D5c** (0.16g) and E-4-methylsulphonylcinnamic acid (0.22g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.44 (3H, s), 2.74 - 2.82 (4H, m), 3.26 (3H, s), 3.63 (2H, s), 7.01 (1H, d), 7.10 (1H, d), 7.47 (2H, m), 7.64 (1H, d), 7.87 (2H, d), 7.98 (2H, d) and 10.32 (1H, br. s); $^m/_z$ (API): 371 (MH^+; 100%)

Example 20c

E-N-methyl-3-[2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ylcarbamoyl)vinyl] benzamide

The title compound (0.17g) was prepared from amine **D5c** (0.16g) and E-3-(3-methylcarbamoylphenyl)acrylic acid (0.21g) according to the procedure of Example 1c.

MS $^m/_z$ (API): 349 (MH^+; 100%)

Example 21c

E-3-(Indazolin-3-yl)-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide

The title compound (0.05) was prepared from amine **D5c** (0.16g) and E-3-indazolin-3-yl acrylic acid (0.19g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.38 (3H, s), 2.65 (2H, m), 2.79 (2H, m), 3.54 (2H, s), 7.09 (1H, d), 7.22 (1H, d), 7.30 (1H, m), 7.47 (2H, m), 7.62 (1H, d), 7.79 (1H, d), 8.09 (1H, d), 10.16 (1H, br, s) and 13.52 (1H, br. s); $^m/_z$ (API): 332 (MH^+; 100%)

Example 22c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylcinnamide

The title compound (0.08g) was prepared from amine **D5c** (0.16g) and E-2-methylcinnamic acid (0.16g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.24 (3H, s), 2.32 (3H, s), 2.48 (2H, t), 2.67 (2H, m), 6.64 (1H, d), 6.97 (1H, d), 7.20 (3H, m), 7.33 (2H, m), 7.49 (1H, d), 7.70 (1H, d) and 10.03 (1H, br. s); $^m/_z$ (API): 307 (MH^+; 100%)

Example 23c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-nitrocinnamide

The title compound (0.04g) was prepared from amine **D5c** (0.16g) and E-2-nitrocinnamic acid (0.19g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.46 (3H, s), 2.68 (2H, s), 2.90 (2H, t), 3.57 (2H, s), 6.45 (1H, d), 7.08 (1H, d), 7.53 (2H, br. s), 7.53 (1H, m), 7.63 (2H, s), 8.04 (1H, d) and 8.10 (1H, d); $^m/_z$ (API): 338 (MH^+; 100%)

Example 24c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-trifluoromethylcinnamide
The title compound (0.05g) was prepared from amine **D5c** (0.16g) and E-2-trifluoromethylcinnamic acid (0.22g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.37 (3H, s), 2.60 (2H, s), 2.80 (2H, m), 3.41 (2H, s), 6.59 (1H, d), 6.95 (1H, d), 7.26 (1H, d), 7.35 - 7.40 (3H, m), 7.54 (1H, d), 7.64 (1H, d), 8.08 (1H, d) and 8.69 (1H, br. s); $^m/_z$ (API): 361 (MH^+; 100%)

Example 25c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-ethoxycinnamide
The title compound (0.06g) was prepared from amine **D5c** (0.16g) and E-2-ethoxycinnamic acid (0.19g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 1.41 (3H, t), 2.63 (2H, t), 2.84 (2H, m), 3.46 (2H, s), 4.40 (2H, q), 6.70 (1H, d), 6.82 - 6.87 (2H, m), 6.99 (1H, d), 7.23 - 7.45 (4H, m), 8.05 (1H, d) and 8.13 (1H, br. s); $^m/_z$ (API): 337 (MH^+; 100%)

Example 26c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-4-fluorocinnamide
The title compound (0.13g) was prepared from amine **D5c** (0.16g) and E-2-chloro-4-fluorocinnamic acid (0.20g) according to the procedure of Example 1c.
^{1}H NMR (250MHz, $CDCl_3$) δ: 2.46 (3H, s), 2.69 (2H, t), 2.89 (2H, m), 3.57 (2H, s), 6.48 (1H, d), 6.99 (1H, dt), 7.08 (1H, d), 7.18 (1H, dd), 7.26 (1H, m), 7.35 (1H, s), 7.43 (1H, s), 7.58 (1H, m) and 8.04 (1H, d); $^m/_z$ (API): 345 (MH^+; 100%)

Example 27c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-6-fluorocinnamide
The title compound (0.06g) was prepared from amine **D5c** (0.16g) and E-2-chloro-6-fluorocinnamic acid (0.20g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.44 (3H, s), 2.67 (2H, t), 2.88 (2H, m), 3.54 (2H, s), 6.83 (1H, d), 6.99 - 7.07 (2H, m), 7.18 - 7.29 (4H, m), 7.41 (1H, s), 7.70(s, 1H and 7.96 (1H, d); $^m/_z$ (API): 345 (MH^+; 100%)

Example 28c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-chlorocinnamide

The title compound (0.02g) was prepared from amine **D11c** (0.16g) and E-4-chlorocinnamic acid (0.18g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.74 - 2.79 (4H, m),3.87 (2H, s), 6.52 (1H, d), 6.91 (1H, d), 7.03 (1H, s), 7.19 (1H, t), 7.35 (2H, d), 7.45 (2H, d), 7.70 (1H, d) and 7.79 (1H, br. s); $^m/_z$ (API): 327, 329 (MH^+; 100%)

Example 29c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-cinnamide

The title compound (0.14g) was prepared from amine **D11c** (0.16g) and cinnamic acid (0.15g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.35 (3H, s), 2.62(2H, t), 2.73 (2H, t), 3.52 (2H, s), 6.66 (1H, d), 6.81 (1H, d), 7.07 (1H, t), 7.31 (3H,. m), 7.44 (3H, m), 7.66 (1H, d) and 7.98 (1H, br. s); $^m/_z$ (API): 293 (MH^+; 100%)

Example 30c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-chlorocinnamide

The title compound (0.06) was prepared from amine **D11c** (0.16g) and 3-chlorocinnamic acid (0.18g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.49 (3H, s), 2.80 (4H, m), 3.64 (2H, s), 6.57 (1H, d), 6.91 (1H, d), 7.19 (1H, t), 7.36 (4H, m), 7.51 (1H, br. s.), 7.68 (1H, d) and 7.79 (1H, br. s);

MS $^m/_z$ (API): 327, 329 (MH^+; 100%)

Example 31c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-chlorocinnamide

The title compound (0.10) was prepared from amine **D11c** (0.16g) and 2-chlorocinnamic acid (0.18g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.75 (4H, m), 3.60 (2H, s), 6.57 (1H, d), 6.91 (1H, d), 7.10 (1H, br. s), 7.19 (1H, t), 7.30 (2H, m), 7.41 (1H, m), 7.62 (1H, br. s), 7.90 (1H, br. s) and 8.13 (1H, d); $^m/_z$ (API): 327, 329 (MH^+; 100%)

Example 32c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-acetylcinnamide hydrochloride

The title compound (0.12) was prepared from amine **D11c** (0.16g) and 3-acetylcinnamic acid (0.19g) according to the procedure of Example 1c. The hydrochloride salt was prepared by treatment of the free base in methanol with diethyl ether/HCl.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.64 (3H, s), 2.74 - 2.81 (4H, m), 3.60 (2H, s), 6.69 (1H, d), 6.90 (1H, d), 7.19 (2H, m), 7.49 (1H, t), 7.69 (1H, m), 7.78 (1H, d), 7.93 (1H, d) and 8.15 (1H, br. s); $^m/_z$ (API): 335 (MH^+; 100%)

Example 33c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-bromocinnamide hydrochloride

The title compound (0.10) was prepared from amine **D11c** (0.16g) and 2-bromocinnamic acid (0.23g) according to the procedure of Example 1c. The hydrochloride salt was prepared by treatment of the free base in methanol with diethyl ether/HCl.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.46 (3H, s), 2.71 - 2.80 (4H, m), 3.59 (2H, s), 6.51 (1H, d), 6.91 (1H, d), 7.07 (1H, br. s.), 7.16 - 7.26 (2H, m), 7.32 (1H, t), 7.60 (1H, br. s.), 7.61 (1H, d), 7.86 (1H, br. s); $^m/_z$ (API): 371, 373 (MH^+; 100%)

Example 34c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylcinnamide hydrochloride

The title compound (0.05) was prepared from amine **D11c** (0.16g) and 2-methylcinnamic acid (0.16g) according to the procedure of Example 1c. The hydrochloride salt was prepared by treatment of the free base in methanol with diethyl ether/HCl.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.46 (3H, s), 2.75 (3H, s), 3.03 (2H, m), 3.13 (2H, m), 3.99 (2H, s), 6.54 (1H, d), 6.89 (1H, d), 7.18 - 7.42 (6H, m), 7.59 (1H, d), 8.04 (1H, d);

MS $^m/_z$ (API): 307 (MH^+; 100%)

Example 35 c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethoxycinnamide

The title compound (0.08g) was prepared from amine **D11c** (0.16g) and 4-ethoxycinnamic acid (0.19g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 1.43 (3H, t), 2.47 (3H, s), 2.74 - 2.80 (4H, m), 3.60 (2H, s), 4.06 (2H, q), 6.42 (1H, d), 6.87 - 6.96 (4H, m), 7.19 (1H, t), 7.47 (2H, d), 7.71 (1H, d) and 7.82 (1H, br. s.); $^m/_z$ (API): 337 (MH^+; 100%)

Example 36c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxycinnamide

The title compound (0.07g) was prepared from amine **D11c** (0.16g) and 2-methoxycinnamic acid (0.18g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.74 - 2.80 (4H, m), 3.60 (2H, s), 3.90 (3H, s), 6.69 (1H, d), 6.88 - 7.02 (4H, m), 7.18 (1H, t), 7.34 (1H, t), 7.50 (1H, d), 7.86 (1H, br. s) and 8.01 (1H, d); $^m/_z$ (API): 323 (MH^+; 100%)

Example 37c

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2-methoxycinnamide

The title compound (0.16g) was prepared from amine **D11c** (0.16g) and 5-bromo-2-methoxycinnamic acid (0.26g) according to the procedure of Example 1c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.71 - 2.81 (4H, m), 3.60 (2H, s), 3.87 (3H, s), 6.62 (1H, d), 6.80 (1H, d), 6.90 (1H, d), 7.00 (1H, br. s), 7.19 (1H, t), 7.41 (1H, dd), 7.61 (1H, br. s), 7.85 (1H, br. s) and 7.95 (1H, d); $^m/_z$ (API): 401, 403 (MH^+; 100%)

Example 38c

E-2-Cyano-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)cinnamide hydrochloride

The title compound (0.11) was prepared from amine D11c (0.16g) and 4-bromo-2-cyanocinnamic acid (0.19g) according to the procedure of Example 1c. The hydrochloride was prepared from the free base in MeOH methanol and diethyl ether/HCl.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.47 (3H, s), 2.74 - 2.80 (4H, m), 3.60 (2H, s), 6.82 - 6.93 (2H, m), 7.16 - 7.22 (2H, m), 7.46 (1H, t), 7.59 - 7.73 (3H, m), 7.83 (1H, br. s.), 7.96 (1H, d); $^m/_z$ (API): 318 (MH^+; 100%)

Example 39c

N-(8-Chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

The title compound (0.13g) was prepared from amine **D13c** (0.21g) and 2-chlorocinnamoyl chloride (0.45g) according to the procedure of Example 2c. ^{1}H NMR (250MHz, $CDCl_3$) δ: 2.97 (2H, m), 3.82 - 3.93 (2H, m), 4.80 (2H, d due to restrited amide rotation), 6.60 (1H, d), 7.16 (1H, t), 7.33 (2H, m), 7.46 (1H, m), 7.67 (1H, m), 7.84 (1H, d), 8.18 (1H, d) and 8.43 (1H, d); $^m/_z$ (API): 443, 445 (MH^+; 100%)

Example 40c

N-(8-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

A solution of N-(8-Chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide (0.2gg) in methanol/water (5ml 9:1) was treated with potassium carbonate (0.38g) and stirred 12h. The mixture was diluted with dichloromethane and washed with water. The organic phase was dried ($MgSO_4$), solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane/methanol/ammonia upto 9:1:0.1 eluant) to give the title compound (0.10g) as a colourless solid. ^{1}H NMR (250MHz, $CDCl_3$) δ: 2.78 (2H, t), 3.10 (2H, t), 4.03 (2H, s), 6.59 (1H, d), 7.07 (1H, d), 7.28 - 7.32 (2H, m), 7.42 (1H, m), 7.66 (1H, m), 7.82 (1H, br. s), 8.16 (1H, d) and 8.31 (1H, d); $^m/_z$ (API): 347, 349 (MH^+; 100%)

Example 41c

N-(8-Chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

A solution of N-(8-Chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide (0.08g) in 37% aqueous formaldehyde (0.63ml) and formic acid (0.34ml) and stirred at 80°C for 3h. Solid sodium hydroxide was added to neutralise the solution and the aqueous phase extracted with dichloromethane. The combined organic extracts were dried (MgSO4) and solvent removed at reduced pressure to give the title compound (0.07g).

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.51 (3H, s), 2.66 (2H, t), 2.90 (2H, t), 3.59 (2H, s), 6.59 (1H, d), 7.07 (1H, d), 7.27 - 7.31 (2H, m), 7.41 (1H, m), 7.64 (1H, m), 7.86 (1H, br. s), 8.14 (1H, d) and 8.27 (1H, d); $^m/_z$ (API): 361, 363 (MH^+; 100%)

Example 42c

N-(8-Bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

The title compound (0.27g) was prepared from amine **D14c** (0.32g) and 2-chlorocinnamoyl chloride according to the procedure of Example 2c.

^{1}H NMR (250MHz, $CDCl_3$) δ: 2.93 - 3.00 (2H, m), 3.82 - 3.92 (2H, m due to restricted rotation), 4.77 (2H, d, due tro restricted rotation) 6.60 (1H, d), 7.17 - 7.36 (3H, m), 7.40 - 7.47 (1H, m), 7.40 - 7.47 (1H, m), 7.87 (1H, m), 8.18 (1H, d) and 8.39 (1H, d);
MS $^m/_z$ (API): 361, 363 (MH^+; 100%)

Example 43c
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl-α-fluorocinnamide
The title compound (0.20g) was prepared from amine **D5c** (0.17g) and Z-α-fluorocinnamic acid (0.19g) according to the procedure of Example 1c. ^{1}H NMR (250MHz, $CDCl_3$) δ:.2.44 (3H, s), 2.67 (2H, t), 2.89 (2H, t), 3.55 (2H, s), 7.03 (1H, d, J = 39Hz), 7.08 (1H, d), 7.29 - 7.41 (4H, m), 7.63 (2H, m) and 8.16 (1H, d); $^m/_z$ (API): 311 (MH^+; 100%)

The following Examples were made in a manner similar to the procedures described in the above Descriptions and Examples

Example 44c
E-N-(8-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide
The title compound (0.36g) was prepared from the trifluoroacetamide of Example 42 (0.681g) according to the method of Example 40.
MS m/z (API^+): 391, 393. $(MH)^+$

Example 45c
E-N-(8-Bromo-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide
The title compound (0.28g) was prepared from the amine of Example 44c (0.361g) according to the method of Example 41c.
MS m/z (API^+): 405, 407 $(MH)^+$

Example 46c
E-N-(2,4,4-Trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide
^{1}H NMR ($CDCl_3$) δ: 1.30 (6H, s), 2.39 (2H, s), 2.41 (3H, s), 3.53 (2H, s), 6.53 (1H, d), 7.40 (7H, m), 7.59 (1H, m), 8.11 (1H, d); m/z: (API^+): 355.2 (MH^+; 100%)

Example 47c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylcinnamide

^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t), 1.35 (6H, s), 2.50 (10H, m), 3.66 (2H, s), 6.49 (1H, d), 7.21 (6H, m), 7.55 (1H, s), 8.05 (1H, d); m/z (API$^+$): 363.3 (MH^+; 100%)

Example 48c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-6-fluorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t), 1.32 (6H, s), 2.40 (2H, s), 2.48 (3H, s), 2.59 (2H, q), 3.56 (2H, s), 6.87 (1H, d), 7.21 (5H, m), 7.67 (1H, s), 7.98 (1H, s); m/z (API$^+$): 401.2 (MH^+; 100%)

Example 49c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-trifluoromethylcinnamide

^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t), 1.34 (6H, s), 2.54 (7H, m), 3.66 (2H, s), 6.59 (1H, d), 7.23 (1H, d), 7.43 (3H, m), 7.69 (2H, t), 8.06 (1H, d); m/z (API$^+$): 417.2 (MH^+; 100%).

Example 50c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-4-fluorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.13 (3H, t), 1.34 (6H, s), 2.53 (7H, m), 3.64 (2H, s), 6.60 (1H, d), 6.99 (2H, m), 7.18 (2H, m), 7.44 (1H, s), 7.60 (2H, m), 8.04 (1H, d); m/z (API$^+$): 401.2 (MH^+; 100%).

Example 51c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.16 (3H, t), 1.33 (6H, s), 2.46 (2H, s), 2.58 (5H, m), 3.62 (2H, s), 6.64 (1H, d), 7.30 (6H, m), 7.63 (1H, s), 8.11 (1H, d); m/z (API$^+$): 383.1 (MH^+; 100%)

Example 52c

E-N-(1,1,2-Trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.44 (6H, s), 2.47 (3H, s), 2.81 - 2.95 (4H, m), 6.62 (1H, d, J = 16 Hz), 6.95 - 7.07 (1H, m), 7.20 - 7.44 (4H, m), 7.55 - 7.63 (1H, m), 7.71 - 7.91 (2H, m), 8.12 (1H, d, J = 16 Hz); m/z (API$^+$): 355, 357 (MH^+)

Example 53c

E-N-(1,2,4,4-Tetramethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, s), 1.28 (3H, s), 1.33 (3H, d, J = 7 Hz), 2.30 (1H, d, J = 12 Hz), 2.43 (3H, s), 2.60 (1H, d, J = 12 Hz), 3.48 (1H, q, J = 7 Hz), 6.59 (1H, d, J = 16 Hz), 7.15 - 7.50 (6H, m), 7.56 (1H, dd, J = 8, 2 Hz), 7.72 (1H, brs), 8.11 (1H, d, J = 16 Hz); m/z (API$^+$): 369, 371 (MH^+).

Example 54c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-ethoxycinnamide

^{1}H NMR ($CDCl_3$) δ: 1.09 (3H, t), 1.34 (6H, d), 1.48 (3H, t), 2.40 (2H, s), 2.46 (5H, m), 3.57 (2H, s), 4.02 (2H, q), 6.89 (4H, m), 7.15 (2H, m), 7.30 (1H, m), 7.45 (1H, dd), 8.08 (1H, d); $^m/_z$ (API$^+$): 393.3 (MH^+; 50%)

Example 55c

E-N-(8-Chloro-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.30 (6H, s), 2.38 (2H, s), 2.47 (3H, s), 3.57 (2H, s), 6.59 (1H, d), 7.29 (3H, m), 7.43 (1H, m), 7.66 (1H, m), 7.81 (1H, s), 8.15 (1H, d), 8.35 (1H, d); $^m/_z$ (API$^+$): 389.0 (M^+; 95%)

Example 56c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxycinnamide

^{1}H NMR ($CDCl_3$) δ: 1.13 (3H, t), 1.34 (6H, s), 2.53 (7H, m), 3.64 (2H, s), 3.92 (1H, s), 6.34 (1H, d), 6.51 (1H, d), 6.91 (1H, d), 7.23 (1H, d), 7.36 (2H, m), 7.61 (2H, m); $^m/_z$ (API$^+$): 413.2 (MH^+; 100%).

Example 57c

E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-cyanocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.16 (3H, t), 1.31 (6H, s), 2.38 (2H, s), 2.47 (3H, s), 2.57 (2H, q), 3.55 (2H, s), 6.88 (1H, d), 7.24 (1H, d), 7.46 (1H, t), 7.68 (5H, m), 7.95 (1H, d); $^m/_z$ (API$^+$): 374.2 (MH^+; 100%).

Example 58c

E-N-(8-Methyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.31 (6H, s), 2.11 (3H, s), 2.38 (2H, s), 2.47 (3H, s), 3.47 (2H, s), 6.61 (1H, d), 7.24 (3H, m), 7.52 (4H, m), 8.11 (1H, d);
MS $^m/_z$ (API$^+$): 369.2 (MH^+; 100%).

Example 59c
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-acetylcinnamide

^{1}H NMR ($CDCl_3$) δ: 1.18 (3H, t), 1.31 (6H, s), 2.40 (3H, s), 2.47 (3H, s), 2.61 (5H, m), 3.57 (2H, s), 6.29 (1H, d), 7.23 (1H, d), 7.45 - 7.72 (6H, m), 8.09 (1H, d);
MS $^m/_z$ (API$^+$): 391.2 (MH^+; 100%).

Example 60c
E-N-(8-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.14 (3H, t), 1.28 (6H, s), 2.56 (2H, q), 2.83 (2H, s), 4.04 (2H, s), 6.60 (1H, d), 7.27 (5H, m), 7.41 (1H, m), 7.64 (1H, s), 8.11 (1H, d);
MS $^m/_z$ (API$^+$): 369.3 (MH^+; 100%)

Example 61c
E-N-(8-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-cyanocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.13 (3H, t), 1.29 (6H, s), 2.55 (2H, q), 2.82 (2H, s), 4.03 (2H, s), 6.89 (1H, d), 7.24 (1H, d), 7.45 (2H, m), 7.61 (2H, m), 7.71 (1H, d), 7.94 (1H, d);
MS $^m/_z$ (API$^+$): 360.2 (MH^+; 100%).

Example 62c
E-N-(8-Chloro-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide

^{1}H NMR ($CDCl_3$) δ: 1.09 (6H, s), 2.42 (3H, s), 2.71 (2H, s), 3.72 (2H, s), 6.59 (1H, d, J = 16 Hz), 7.03 (1H, d, J = 8 Hz), 7.23 – 7.40 (2H, m), 7.44 (1H, m), 7.67 (1H, m), 7.82 (1H, brs), 8.15 (1H, d, J = 16 Hz), 8.30 (1H, brd, J = 8 Hz);m/z (API$^+$): 389.3 (MH^+; 100%)

Example 63c

E-N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide
MS $^{m}/_{z}$ (API^{+}): 392.9 (MH^{+}; 100%, $C_{18}H_{16}BrClN_2O$ requires M^{+} 391).

Example 64c
E-N-(5,6,7,8-Tetrahydro-6-methyl[1,6]naphthyridin-3-yl)-cinnamide
Prepared from *trans*-cinnamic acid and **D9c**
MS m/z (API^{+}): 294 (MH^{+}; 100%, $C_{18}H_{19}N_3O$ requires M^{+} 293).

Example 65c
E-N-(5,6,7,8-Tetrahydro-6,8,8-trimethyl[1,6]naphthyridin-3-yl)-2-chlorocinnamide hydrochloride
Prepared from **D47c** and *trans*-2-chlorocinnamic acid (183mg; 1.0 mmol) and isolated as a white powder (86mg; 22%).
^{1}H NMR [free base] (250 MHz; CD_3OD) δ: 1.24 (6H, s), 2.36 (3H, s), 2.50 (2H, s) 3.50 (2H, s), 6.68 (1H, d, J = 16 Hz), 7.17 – 7.37 (3H, m), 7.64 (1H, m), 7.83 (1H, d, J = 2 Hz), 7.98 (1H, d, J = 16 Hz), 8.50 (1H, d, J = 2 Hz);
m/z (API^{+}): 356.1 $(MH)^{+}$, 378.1 $(M+Na)^{+}$.

Description 1rc
E-7-(2-Ethoxycarbonylvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester
(a) A mixture of 7-bromo-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (1.0g), palladium (II) acetate 0.037g), tris(o-tolyl)phosphine (0.1g) triethylamine (0.67ml) and ethyl acrylate (0.52ml) in acetonitrile (2ml) was boiled for 4 h. After cooling to room temperature the mixture was diluted with ethyl acetate, washed with water and brine dried (MgSO4) and solvent removed at reduced pressure. The residue was column chromatographed (silca gel, ethyl acetate/hexane) to give after combining of appropriate fractions 7-(2-ethoxycarbonylvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (0.51g).
^{1}H NMR (250MHz $CDCl_3$) δ: 1.31 (3H, t), 2.85 (2H, t), 3.65 (2H, t), 4.26 (2H, q), 4.58 (2H, s), 6.40 (1H, d, J = 16Hz), 7.15 (1H, d), 7.26 (1H, s), 7.33 (1H, d) and 7.64 (1H, d, J = 16Hz).

Description 2rc
E-7-(2-Carboxyvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester

A solution of 7-(2-ethoxycarbonylvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (1.0g) in ethanol/water (30ml, 2:1) containing potassium hydroxide (0.34g) was stirred for 16h. Solvent was reduced to low volume and partitioned between ethyl acetate and water. The pH of the aquous phase was adjusted to 1 by the addition of 5N HCl, the organic phase separated and washed with brine, dried (MgSO4) and solvent removed at reduced pressure to give -7-(2-carboxyvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert butyl ester (0.76g).
MS m/z (API$^+$): 204 (MH^+; 100%)

Description 3rc
E-7-Bromo-(2-Methyl-1,2,3,4-tetrahydroisoquinoline)
A solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline (13.0g) in formic acid (21ml) was treated with 40% formalin and heated at 80°C for 2h. After cooling to room temperature, the reaction mixture was neutralised with sodium hydroxide (20g) and extracted with dichloromethane. The organic phase was washed with brine dried (MgSO4) and solvent removed at reduced pressure to give the title compound (13.0g) as an oil.

Description 4rc
E-7-(2-Ethoxycarbonylvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline
The title compound was prepared from 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline and ethyl acrylate in 30% yield according to the method of Description 1rc.

Description 5rc
E-7-(2-Carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline
E-7-(2-ethoxycarbonylvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline) (4.59g) in methanol (100ml) was warmed to 50°C and sodium hydroxide (2N, 50ml) added. The mixture was stirred at 50°C for 12h, stood at room temperature for 24h and then neutralised with hydrochloric acid (2N, 50ml). Solvent was removed at reduced pressure to give a final volume of 80ml. The title compound (2.4g) crystallised on standing.

Example 1rc
E-N-(4-Methoxyphenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
(a) E--7-(2-carboxyvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert butyl ester (0.47g), hydroxybenzotriazole (0.02g), 4-anisidine (0.19g) in DMF (5ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.30g). The

mixture was stirred for 16h, diluted with ethyl acetate, washed with water, 2N HCl, aqueous sodium carbonate and brine to give E-7-(2-carboxyvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert butyl ester(0.59g).
m/z(API$^+$): 409 (MH^+)

(b) A solution of E-7-[2-(4-methoxyphenylcarbamoyl)vinyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (0.48g) in dichloromethane (6ml) was treated with trifluoroacetic acid and stirred for 16h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel 0 - 10% {9:1 methanol/ammonia} in dichloromethane) to give the title compound (0.24g) after trituration with diethyl ether.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.82 (2H, t), 3.17 (2H, t), 3.80 (3H, s), 4.05 (2H, s), 6.67 (1H, d), 6.86 (2H, d), 7.11 (1H, d), 7.17 (1H, s), 7.33 (1H, d), 7.61 (3H, m) and 9.09 (1H, br. s); m/z(API$^+$): 309 (MH^+; 100%)

Example 2rc
E-N-Phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
(a) From E-7-(2-carboxyvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert butyl ester (0.48g) and aniline (0.14g), E-7-(2-phenylcarbamoylvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (0.44g) was prepared according to the method of Example 1rc(a).
^{1}H NMR (250MHz, $CDCl_3$) δ;2.84 (2H, t), 3.65 (2H, t), 4.57 (2H, s), 6.52 (1H, d), 7.12 - 7.64 (8H, m) and 7.71 (1H, d).
(b) From E-7-(2-phenylcarbamoylvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (0.43g), the title compound (0.17g) isolated as a colourless solid was prepared according to the method of Example 1rc(b).
^{1}H NMR (250MHz, d^{6}DMSO) δ; 2.71 (2H, t), 2.99 (2H, t), 3.90 (2H, s), 6.73 (1H, d), 7.00 (1H, t), 7.12 (1H, d), 7.24 - 7.35 (4H, m), 7.45 (1H, d), 7.63 (2H, d) and 10.12 (1H, s);
MS m/z(API$^+$): 279 (MH^+; 100%)

Example 3rc
E-N-Phenyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
E-N-Phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide (0.13g) was heated for 150 min in a mixture of formic acid (0.54ml) and 37% formaldehyde (1ml). After cooling the mixture was neutralised by the addition of solid sodium hydroxide and partitioned between dichloromethane and water. The organic phase was washed with 2N sodium hydroxide, water, brine and dried ($MgSO_4$). Solvent was removed at reduced pressure and the residue column chromatographed (silica

gel 0 - 10% {9:1methanol/ammonia} in dichloromethane) to give the title compound (0.05g) as a colourless solid.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.47 (3H, s), 2.69 (2H, t), 2.94 (2H, t), 3.57 (2H, s), 6.50 (1H, d), 7.10 - 7.63 (8H, m) and 7.72 (1H, d); m/z(API$^+$): 293(MH^+; 100%)

Example 4rc
E-N-Phenyl-3-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
E-N-phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide (0.28g), benzaldehyde (0.1ml), acetic acid (0.057ml) and methanol (20ml) were combined and treated with sodium cyanoborohydride (0.63g). The mixture was stirred for 16h, solvent was removed *in vacuo* and the residue column was chromatographed (silica gel 0 - 10% {9:1 methanol-ammonia} in dichloromethane) to give the title compound (0.23g) as a colourless foam.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.79 (2H, t), 2.95 (2H, t), 3.65 (2H, s), 3.73 (2H, s), 6.48 (1H, d), 7.10 - 7.63 (11H, m) 7.62 (2H, d,) and 7.69 (1H, d); m/z(API$^+$): 369(MH^+; 100%)

Example 5rc
E-N-Phenyl-3-(2-n-propyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-N-phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide (0.28g) and propionaldehyde (0.07ml), the title compound (0.22g) isolated as a colourless solid was prepared according to the method of Example 4rc.
^{1}H NMR (250MHz, $CDCl_3$) δ; 1.05 (3H, t), 1.78 (2H, m), 2.87 (2H, t), 3.06 (2H, d), 3.14 (2H, d), 4.13 (2H, s), 6.80 (1H, d), 7.05 -7.37 (6H, m), 7.58 (1H, d), 7.75 (2H, d) and 9.24 (1H, s); m/z(API$^+$): 321(MH^+; 100%)

Example 6rc
E-N-Phenyl-3-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-N-phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide (0.28g) and acetaldehyde (0.06ml), the title compound (0.88g) isolated as a colourless solid was prepared according to the method of Example 4rc.
^{1}H NMR (250MHz, $CDCl_3$) δ; 1.20 (3H, t), 2.60 (2H, q), 2.74 (2H, t), 2.93 (2H, t), 3.62 (2H, s), 6.50 (1H, d), 7.12 (2H, t), 7.19 (1H, s), 7.26 - 7.38 (3H, m) 7.61 (2H, d) and 7.69(1H, d); m/z(API$^+$): 307(MH^+; 100%)

Example 7rc
E-N-(3-Cyanophenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
(a) From E-7-(2-carboxyvinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert butyl ester (1.01g) and 3-aminobenzonitrile (0.39g), E-7-[2-(3-

cyanophenyl)carbamoylvinyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (0.41g) was prepared according to the method of Example 1rc(a).
m/z(API$^+$): 304 (MH$^+$- tertbutoxycarbonyl; 100%)
(b) From E-7-[2-(3-cyanophenyl)carbamoylvinyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert* butyl ester (0.38g), the title compound (0.08g) isolated as a colourless solid was prepared according to the method of Example 1rc(b).
^{1}H NMR (250MHz, d^{6}DMSO) δ; 2.73(t, 2H), 2.98(t, 2H), 3.90(s, 2H), 6.75(d, 1H), 7.15(d, 1H), 7.30(s, 1H), 7.39(d, 1H), 7.58(d, 1H), 7.85(m, 1H), 8.25(s, 1H) and 10.51(s, 1H);
MS m/z(API$^+$): 304 (MH$^+$; 100%)

Example 8rc
E-N-(3-Cyanophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-N-(3-cyanophenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide (0.06g) the title compound (0.03g), isolated as a colourless solid was prepared according to the method of Example 3rc.
^{1}H NMR (250MHz, d^{6}DMSO) δ; 2.35 (3H, s), 2.60 (2H, t), 2.84 (2H, t), 3.51 (2H, s), 6.74 (1H, d), 7.18 (1H, d), 7.31 (1H, s), 7.40 (1H, d), 7.51 - 7.59 (3H, m) 7.87 (1H, d), 8.21 (1H, s) and 10.49 (1H, s).(1H, d), 7.85 (1H, m), 8.25 (1H, s) and 10.51 (1H, s);
MS m/z(API$^+$): 318 (MH$^+$; 100%)

Example 9rc
E-N-(2-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 2-chloroaniline (0.13g) the title compound (0.03g) was prepared according to the method of Example 1rc(a) omitting the acid wash.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.50 (3H, s), 2.74 (2H, t), 2.96 (2H, t), 3.63 (2H, s), 6.54 (1H, d), 7.06 (1H, t), 7.15 (1H, d), 7.23 - 7.46 (4H, m), 7.71 (1H, d), 7.78 (1H, br. s.) and 8.54 (1H, d); m/z(API$^+$): 327(MH$^+$; 100%)

Example 10rc
E-N-(2-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 2-methoxyaniline (0.12g), the title compound (0.13g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, d^{6}DMSO) δ; 2.44 (3H, s), 2.66 (2H, t), 2.91 (2H, t), 3.55 (2H, s), 3.87 (3H, s), 6.55 (1H, d), 6.86 (1H, dd), 6.93 - 7.07 (3H, m), 7.17 (1H, s), 7.29 (1H, t), 7.66 (1H, d), 7.99 (1H, br. s.) and 8.50 (1H, d); m/z(API$^+$): 323 (MH$^+$; 100%)

Example 11rc

E-N-(3-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-methoxyaniline (0.12g), the title compound (0.10g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.44 (3H, s), 2.67 (2H, m), 2.90 (2H, m), 3.51 (2H, s), 3.78 (3H, s), 6.54 (1H, d), 6.67 (1H, d), 7.02 - 7.26 (5H, m), 7.46 (1H, s), 7.66 (1H, d) and 7.98 (1H, s); m/z(API$^+$): 322 (MH$^+$; 100%)

Example 12rc

E-N-(3-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-chloroaniline (0.13g), the title compound (0.09g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.79 (3H, s), 3.08 (2H, m), 3.16 (2H, m), 4.06 (2H, s), 6.47 (1H, d), 6.95 (1H, d), 6.97 (1H, s), 7.14 (2H, dt), 7.20 - 7.29 (1H, m), 7.37 (1H, d), 7.69 (1H, m), 7.94 (1H, m) and 9.43 (1H, br. s.); m/z(API$^+$): 327 (MH$^+$; 100%)

Example 13rc

E-N-(4-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-chloroaniline, the title compound (0.09g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, d^{6}DMSO) δ; 2.41 (3H, s), 2.69 (2H, m), 2.86 (2H, m), 3.59 (2H, s), 6.76 (1H, d), 7.18 (1H, d), 7.30 (1H, s), 7.37 - 7.40 (3H, m), 7.54 (1H, d), 7.79 (2H, d) and 10.34 (1H, br. s); m/z(API$^+$): 327 (MH$^+$; 100%)

Example 14rc

E-N-Methyl-N-benzyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and N-methylbenzylamine (0.12g), the title compound (0.16g) was prepared according to the method of Example 1rc(a) omitting the acid wash.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.46 (3H, d), 2.70 (2H, m), 2.91 (2H, m), 3.07 (3H, d), 3.57 (2H, d), 4.69 (2H, d), 6.85 (1H, t), 7.06 - 7.38 (8H, m) and 7.72 (1H, d); MS m/z(API$^+$): 320 (MH^+; 100%)

Example 15rc
E-N-(3-Nitrophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-nitroaniline (0.14g), the title compound (0.04g) was prepared according to the method of Example 1rc(a) omitting the acid wash.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.46(3H, s), 2.73 (2H, m), 2.89 (2H, m), 3.54 (2H, s), 4.69 (2H, d), 6.54 (1H, d), 7.03 (2H, m), 7.19 (1H, d), 7.43 (1H, t), 7.64 (1H, d), 7.92 (1H, d), 8.10 (1H, d), 8.48 (1H, s) and 8.88 (1H, br s.); m/z(API$^+$): 338 (MH^+; 100%)

Example 16rc
E-N-Methyl-N-phenyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and N-methylaniline (0.11g), the title compound (0.15g) was prepared according to the method of Example 1rc(a) omitting the acid wash.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.42 (3H, s), 2.64 (2H, t), 2.87 (2H, t), 3.40 (3H, s), 3.50 (2H, s), 6.30 (1H, d), 6.96 - 7.10 (2H, m), 7.21 - 7.26 (2H, m), 7.34 - 7.49 (2H, m) and 7.62 (1H, d); m/z(API$^+$): 307 (MH^+; 100%)

Example 17rc
E-N-(3-Carbomethoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-carbomethoxyaniline (0.15g), the title compound (0.07g) was prepared according to the method of Example 1rc(a) omitting the acid wash.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.57 (3H, s), 2.79 (2H, m), 2.96 (2H, m), 3.73 (2H, s), 3.91 (3H, s), 6.49 (1H, d), 7.04 (1H, d), 7.08 (1H, s), 7.20 (1H, d), 7.45 (1H, t), 7.59 (1H, d), 7.78 (1H, d), 8.06 (1H, d), 8.245 (1H, s) and 8.50 (1H, s); m/z(API$^+$): 351 (MH^+; 100%)

Example 18rc

E-N-Methyl-3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acryloylamino]benzamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-N-methylcarboxamidoaniline (0.15g), the title compound (0.07g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, d^6-DMSO) δ; 2.79 (3H, d), 2.83 - 2.94 (4H, m), 3.17 (3H, s), 3.72 (2H, s), 6.56 and 6.84 (1H, d), 6.99 (1H, t), 7.14 - 7.59 (5H, m), 7.88 (1H, t), 8.13 (1H, s), 8.44 (1H, m) and 10.46 (1H, s); m/z(API$^+$): 350 (MH^+)

Example 19rc

E-N-(3-N-Methylsulphonylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide

A solution of E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) in dichloromethane (10ml) was treated with oxalyl chloride (0.30ml) and dimethylformamide (2 drops). The mixture was stirred for 2h, solvent removed at reduced pressure and the residue treated sequentialy with 3-methylsulphonylaniline hydrochloride (0.21g), tetrahydrofuran (20ml) and triethylamine (1ml). The reaction mixture was stirred for 16h, diluted with ethyl acetate and washed with water. The organic phase was dried (MgSO4) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 5% methanol/dichloromethane) to give the title compound (0.07g).

^{1}H NMR (250MHz, d^6-DMSO with D_2O shake) δ; 2.69 (3H, s), 3.03 (2H, m), 3.12 (2H, m), 3.20 (3H, s), 4.03 (2H, s), 6.81 (1H, d), 7.30 (1H, d), 7.43 (1H, s), 7.53 - 7.65 (4H, m), 7.91 (1H, br. s) and 8.38 (1H, s); m/z(API$^+$): 371 (MH^+)

Example 20rc

E-N-(1,3-Oxazol-5-ylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 1,3-oxazol-5-ylaniline (0.16g), the title compound (0.15g) was prepared according to the method of Example 19rc omitting triethylamine.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.43 (3H, s), 2.67 (2H, t), 2.91 (2H, t), 3.51 (2H, s), 6.57 (1H, d), 7.04 - 7.10 (2H, m), 7.24 - 7.37 (3H, m), 7.60 (1H, m), 7.73 (1H, d), 7.84 (1H, s), 8.03 (1H, s) and 8.17 (1H, s); m/z(API$^+$): 360 (MH^+; 100%)

Example 21rc

E-N-(3-Acetylaminophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-acetylaminoaniline (0.15g), the title compound (0.13g) was prepared according to the method of Example 19rc omitting triethylamine.
^{1}H NMR (250MHz, $CDCl_3$). 2.04 (3H, s), 2.39 (3H, s), 2.63 (2H, m), 2.86 (2H, m), 3.49 (2H, s), 6.54 (1H, d), 6.96 - 7.37 (5H, m), 7.56 (1H, d), 7.82 (1H, s), 8.27 (1H, s) and 8.65 (1H, s); m/z(API$^+$): 350 (MH^+; 100%)

Example 22rc
E-N-(3-Ethylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-ethylaniline (0.12g), the title compound (0.10g) was prepared according to the method of Example 19rc omitting triethylamine.
^{1}H NMR (250MHz, $CDCl_3$) δ; 1.20 (3H, t), 2.43 (3H, s), 2.60 (2H, q), 2.67 (2H, m), 2.90 (2H, m), 3.51 (2H, s), 6.55 (1H, d), 6.94 (1H, d), 7.04 - 7.26 (4H, m), 7.42 - 7.50 (2H, m), 7.68 (1H, d) and 7.89 (1H, s); m/z(API$^+$): 321 (MH^+; 100%)

Example 23rc
E-N-(3-Methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-methylaniline (0.12g), the title compound (0.09g) was prepared according to the method of Example 19rc omitting triethylamine.
^{1}H NMR (250MHz, $CDCl_3$) δ 2.32 (3H, s), 2.45 (3H, s), 2.68 (2H, t), 2.91 (2H, m), 3.52 (2H, s), 6.53 (1H, d), 6.91 (1H, d), 7.05 - 7.28 (4H, m), 7.38 (1H, d), 7.48 (1H, s), 7.68 (1H, d) and 7.69 (1H, s); m/z(API$^+$): 307 (MH^+; 100%)

Example 24rc
E-N-(3-*tert*-Butylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide
From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-*tert*butylaniline (0.15g), the title compound (0.11g) was prepared according to the method of Example 19rc omitting triethylamine.
^{1}H NMR (250MHz, $CDCl_3$) δ; 1.28 (9H, s), 2.42 (3H, s), 2.65 (2H, t), 2.89 (2H, m), 3.48 (2H, s), 6.60 (1H, d), 6.91 (1H, d), 7.01 - 7.23 (4H, m), 7.64 - 7.69 (2H, m), 8.22 (1H, s);
MS m/z(API$^+$): 349 (MH^+; 100%)

Example 25rc

E-N-(4-Fluorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-fluoroaniline (0.12g), the title compound (0.15g) was prepared according to the method of Example 19rc omitting triethylamine.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.44 (3H, s), 2.67 (2H, t), 2.91 (2H, t), 3.52 (2H, s), 6.50 (1H, d), 6.80 - 7.10 (4H, m), 7.25 (1H, d), 7.41 (2H, br.m.), 7.67 (1H, d) and 7.82 (1H, br. s); m/z(API$^+$): 311 (MH^+; 100%)

Example 26rc

E-N-(4-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-methoxyaniline (0.12g), the title compound (0.15g) was prepared according to the method of Example 19rc omitting triethylamine.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.45 (3H, s), 2.68 (2H, t), 2.92 (2H, t), 3.55 (2H, s), 3.79 (3H, s), 6.49 (1H, d), 6.87 (2H, d), 7.11 - 7.63 (3H, d), 7.52 (2H, br s) and 7.66 (1H, d);

MS m/z(API$^+$): 323 (MH^+; 100%)

Example 27rc

E-N-(4-Carbomethoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-carbomethoxyaniline (0.15g), the title compound (0.19g) was prepared according to the method of Example 19rc omitting triethylamine.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.46 (3H, s), 2.69 (2H, t), 2.93 (2H, t), 3.55 (2H, s), 3.90 (3H, s), 6.52 (1H, d), 7.09 - 7.31 (4H, m), 7.68 - 7.73 (2H, m), 7.80 (1H, d) and 8.01 (2H, d); m/z(API$^+$): 351 (MH^+; 100%)

Example 28rc

E-N-(4-Cyanophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-aminobenzonitrile (0.12g), the title compound (0.03g) was prepared according to the method of Example 19rc omitting triethylamine.

^{1}H NMR (250MHz, $CDCl_3$) δ; 2.50 (3H, s), 2.75 (2H, t), 2.96 (2H, t), 3.61 (2H, s), 6.52 (1H, d), 7.15 (1H, d), 7.26 (1H, s), 7.30 (1H, d), 7.61 (2H, d), 7.69 (1H, d), 7.78 (2H, d) and 7.95 (1H, s); m/z(API$^+$): 318 (MH^+; 100%)

Example 29rc
E-N-(4-Nitrophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-nitroaniline (0.14g), the title compound (0.09g) was prepared according to the method of Example 19rc omitting triethylamine.
^{1}H NMR (250MHz, d^6-DMSO) δ; 2.50 (3H, s), 2.60 (2H, t), 2.82 (2H, m), 3.50 (2H, s), 6.47 (1H, d), 7.18 (1H, d), 7.32 (1H, s), 7.40 (1H, d), 7.64 (1H, d), 7.93 (2H, d), 8.24 (2H, d), 10.76 (1H, br. s); m/z(API$^+$): 337 (MH^+; 100%)

Example 30rc
E-N-(4-Methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 4-toluidine (0.11g), the title compound (0.09g) was prepared according to the method of Example 19rc omitting triethylamine.
^{1}H NMR (250MHz, d^6-DMSO) 2.31 (3H, s), 2.44 (3H, s), 2.67 (2H, m), 2.91 (2H, m), 3.51 (2H, s), 6.53 (1H, d), 6.99 - 7.13 (4H, m), 7.24 (1H, d), 7.51 (2H, d), 7.66 (1H, d) and 7.92 (1H, d); m/z(API$^+$): 306 (MH^+; 100%)

Example 31rc
E-N-(3-Methoxy-5-trifluoromethylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3-methoxy-5-trifluoromethylaniline (0.19g), the title compound (0.16g) was prepared according to the method of Example 19rc.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.46 (3H, s), 2.67 (2H, t), 2.93 (2H, m), 3.56 (2H, s), 3.83 (3H, s), 6.49 (1H, d), 6.88 (1H, s), 7.10 (1H, d), 7.15 (1H, s), 7.26 - 7.31 (2H, m), 7.66 (1H, d) and 7.73 (1H, d); m/z(API$^+$): 390 (MH^+; 100%)

Example 32rc
E-1-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 1,2,3,4-tetrahydroisoquinoline (0.13g) the title compound (0.07g) was prepared according to the method of Example 1rc(a) omitting the acid wash.
^{1}H NMR (250MHz, $CDCl_3$) δ; 2.47 (3H, s), 2.70 (2H, t), 2.94 (4H, m), 3.60 (2H, s), 3.88 (2H, m), 6.89 (1H, d), 7.11 - 7.21 (6H, m), 7.34 (1H, d) and 7.67 (1H, d);

m/z(API$^+$): 333(MH$^+$; 100%)

Example 33rc

E-1-(3,4-Dihydro-2H- quinolin-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 1,2,3,4-tetrahydroquinoline (0.13g) the title compound (0.07g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, d^6-DMSO) 1.69 (2H, t), 2.11 (3H, s), 2.33 (2H, m), 2.37 (2H, m), 2.52 (2H, t), 3.23 (2H, s), 3.59 (2H, t), 6.64 (1H, d), 6.91 - 7.10 (7H, m) and 7.31 (1H, d);

MS m/z(API$^+$): 333(MH$^+$; 100%)

Example 34rc

E-1-(3,3-Dimethyl-2,3-dihydroindol-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and 3,3-dimethylindoline (0.15g) the title compound (0.06g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, $CDCl_3$) 1.39 (6H, s), 2.47 (3H, s), 2.70 (2H, t), 2.92 (2H, m), 3.61 (2H, s), 4.00 (2H, s), 6.78 (1H, d), 7.04 - 7.26 (5H, m), 7.36 (1H, d), 7.78 (1H, d) and 8.31 (1H, br. s.); m/z(API$^+$): 346(MH$^+$; 100%)

Example 35rc

E-1-(2,3-Dihydroindol-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone

From E-7-(2-carboxyvinyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.22g) and indoline (0.12g) the title compound (0.11g) was prepared according to the method of Example 1rc(a) omitting the acid wash.

^{1}H NMR (250MHz, $CDCl_3$) 2.48 (3H, s), 2.71 (2H, t), 2.95 (2H, t), 3.61 (2H, s), 4.28 (2H, t), 6.84 (1H, d), 7.03 (1H, t), 7.13 (1H, d), 7.20 (3H., m), 7.35 (1H, d), 7.78 (1H, d) and 8.36 (1H, br s); m/z(API$^+$): 318(MH$^+$; 100%)

PHARMACOGICAL DATA

1. Binding Assay Method

Internation al Application Publication Number WO 92/22293 (SmithKline Beecham) discloses compounds having anti-convulsant activity, including *inter alia* the compound *trans*-(+)-6-acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (hereinafter referred to as Compound A). It has

been found that the compounds of WO 92/22293 bind to a novel receptor obtainable from rat forebrain tissue, as described in WO 96/18650 (SmithKline Beecham). The affinity of test compounds to the novel receptor site is assessed as follows.

Method

Whole forebrain tissue is obtained from rats. The tissue is first homogenised in buffer (usually 50mM Tris/HCl, pH 7.4). The homogenised tissue is washed by centrifugation and resuspension in the same buffer, then stored at -70°C until used.

To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A dissolved in buffer. The final concentration of [3H]-Compound A in the mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting in a liquid scintillation counter.

In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 μM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

The affinity of the binding of test compounds to the novel site can be estimated by incubating together [3H]-Compound A and tissue in the presence of a range of concentrations of the compound to be tested. The decrease in the level of specific [3H]-Compound A binding as a result of competition by increasing concentrations of the compound under test is plotted graphically, and non-linear regression analysis of the resultant curve is used to provide an estimate of compound affinity in terms of pKi value.

Results

Compounds of this invention were active in this test with pKi values greater than 6. For example, compounds of Examples *9c, 27c and 2rc* gave pKi values greater than 7.5.

2. MEST Test

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties[1]. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method

Mice (naive male, Charles River, U.K. CD-1 strain, 25 - 30g) are randomly assigned to groups of 10 - 20 and dosed orally or intraperitoneally at a dose volume of 10 ml/kg with various doses of compound (0.3 - 300 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a single electroshock (0.1 sec, 50Hz, sine wave form) administered via corneal electrodes. The mean current and standard error required to induce a tonic seizure in 50% (CC_{50}) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)[2]. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)[3].

In control animals the CC_{50} is usually 14 - 18 mA. Hence the first animal in the control group is subjected to a current of 16 mA. If a tonic seizure does not ensue, the current is increased for a subsequent mouse. If a tonic convulsion does occur, then the current is decreased, and so on until all the animals in the group have been tested.

The percentage increase or decrease in CC_{50} for each group compared to the control is calculated.

Studies are carried out using a Hugo Sachs Electronik Constant Current Shock Generator with totally variable control of shock level from 0 to 300 mA and steps of 2 mA are usually used.

Drugs are suspended in 1% methyl cellulose.

References

1. Loscher, W. and Schmidt, D. (1988). Epilepsy Res., **2**, 145-181
2. Dixon, W.J. and Mood, A.M. (1948). J. Amer. Stat. Assn., **43**, 109-126
3. Litchfield, J.T. and Wilcoxon, F.(1949). J. Pharmacol. exp. Ther., **96**, 99-113

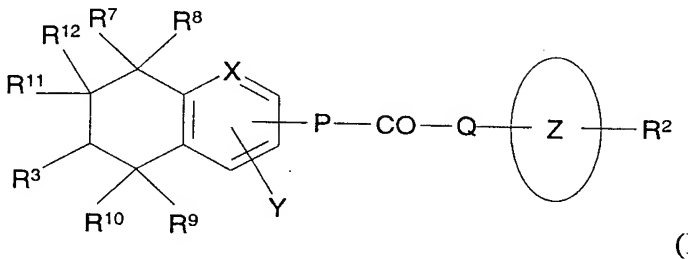
Results

Compounds of this invention dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing show an increase in seizure threshold. For example, at a dose of 10 mg/kg p.o. the compounds of Examples *9c, 27c and*

2rc showed statistically significant increases of *245, 192 and 140* % respectively.

Claims

1. Accordingly, the present invention provides a compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

in which

Z is a carbocyclic or heterocyclic or a fused carbocyclic or heterocyclic ring containing at least one aromatic ring;

X is CHor N;

Y is hydrogen, C_{1-6}alkyl, or a halogen;

P is -CH=CH- and Q is $-NR^1-$, or;

P is -CH=CH- and Q is $-NR^1CH_2-$, or;

P is -NH- and Q is $-CR^{1a}=CH-$;

R^1 ishydrogen, phenylC_{1-6} alkyl, or C_{1-6} alkyl;

R^{1a} is hydrogen, halogen, phenylC_{1-6} alkyl, or C_{1-6} alkyl;

R^2 ishydrogen or up to three substituents selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, CF_3SO_2, trifluoromethyldiazirinyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkylO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, C_{1-6}alkylS-, C_{1-6}alkylSO_2-, or 1,3-oxazol-5-yl(C_{1-4}alkyl)$_2NSO_2$-, (C_{1-4}alkyl)$NHSO_2$-, (C_{1-4}alkyl)$_2$NCO-, (C_{1-4}alkyl)NHCO- or $CONR^4R^5$, CO_2R^4;

or $-NR^4R^6$ or $NHCOR^4$

where R^4 and R^5 are each independently hydrogen or C_{1-4} alkyl, and;

R^6 is hydrogen, C_{1-4}alkyl, formyl, $-CO_2C_{1-4}$alkyl, or $-COC_{1-4}$alkyl;

or two R^2 groups are linked together to form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O or a heterocyclic ring that is saturated or unsaturated;

or when P is -CH=CH- and Q is -NR^1CH_2-, R^1 and an R^2 are linked together to form a saturated or unsaturated carbocyclic or heterocyclic ring;
or when P is -CH=CH- and Q is -NR^1-, R^1 and an R^2 are linked together to form a saturated or unsaturated carbocyclic or heterocyclic ring, and;

R^3 is hydrogen, phenylC_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkylOCO-, C_{1-6}alkylCO-, formyl, CF_3CO- or C_{1-6}alkylSO_2-, hydroxyC_{1-6}alkyl, or C_{1-6}alkoxyC_{1-6}alkyl.

R^7 is hydrogen or C_{1-6} alkyl;

R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

R^{10} is hydrogen or C_{1-6} alkyl;

R^{11} is hydrogen or C_{1-6} alkyl, and;

R^{12} is hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 wherein
P is -CH=CH- or Q is CR^{1a}=CH and the compound is the E isomer.

3. A compound according to claim 1 or 2 wherein
R^1 is hydrogen, fluoro, methyl, ethyl or propyl;
R^2 is hydrogen or one or more of methyl, ethyl, *n*-butyl, phenyl, *iso*-propyl, *t*-butyl, methoxy, ethoxy, n-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amino, acetylamino, methylthio, oxazolo, methylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl, and;
R^3 is hydrogen, methyl, ethyl, propyl, benzyl, *t*-butyloxycarbonyl or trifluoroacetyl.

4. A compound according to any one of claims 1 to 3 wherein
R^1 is hydrogen, fluoro or methyl;
R^2 is hydrogen or one or more of methyl, ethyl, *t*-butyl, methoxy, methoxycarbonyl, methylcarbonyl, ethylcarbonyl, methylamido, acetylamino, methylsulfonyl, oxazole, trifluoromethyl, cyano, chloro, fluoro, or nitro;
R^3 is hydrogen, methyl, ethyl, *n*-propyl, benzyl or *t*-butyloxycarbonyl.

5. A compound of formula (I) according to claim 1 selected from

E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-nitrocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-trifluoromethylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cinnamide hydrochloride;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-α-methylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxycinnamide;
E-N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-3-yl)-3-phenylacrylamide;
E-3-Furan-2-yl-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-thiophen-2-ylacrylamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2, 4-dichlorocinnamide;
Z-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxycinnamide;
E-3-Indolin-5-yl-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide;
E-3-(1-Methyl-Indolin-2-yl)-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methylsulphonylcinnamide;
E-N-methyl-3-[2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ylcarbamoyl)vinyl] benzamide;
E-3-(Indazolin-3-yl)-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-acrylamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-nitrocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-trifluoromethylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-ethoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-4-fluorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-6-fluorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-cinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-acetylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-bromocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylcinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxycinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2-methoxycinnamide;

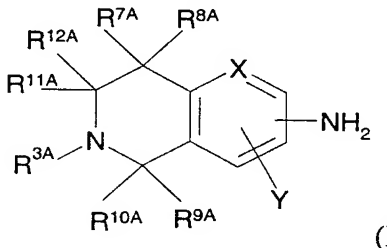
E-2-Cyano-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)cinnamide;
N-(8-Chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
N-(8-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
N-(8-Chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
N-(8-Bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl-α-fluorocinnamide;
E-N-(8-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Bromo-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(2,4,4-Trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylcinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-6-fluorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-trifluoromethylcinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chloro-4-fluorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(1,1,2-Trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(1,2,4,4-Tetramethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-ethoxycinnamide;
E-N-(8-Chloro-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxycinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-cyanocinnamide;
E-N-(8-Methyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-acetylcinnamide;
E-N-(8-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(8-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-cyanocinnamide;
E-N-(8-Chloro-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;

E-N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-chlorocinnamide;
E-N-(5,6,7,8-Tetrahydro-6-methyl[1,6]naphthyridin-3-yl)-cinnamide, and;
E-N-(5,6,7,8-Tetrahydro-6,8,8-trimethyl[1,6]naphthyridin-3-yl)-2-chlorocinnamide.

6. A compound of formula (I) according to claim 1 selected from
E-N-(4-Methoxyphenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-n-propyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Phenyl-3-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Cyanophenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Cyanophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(2-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(2-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Chlorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Methyl-N-benzyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Nitrophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Methyl-N-phenyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Carbomethoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-Methyl-3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acryloylamino]benzamide;
E-N-(3-N-Methylsulphonylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide;
E-N-(1,3-Oxazol-5-ylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Acetylaminophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide;
E-N-(3-Ethylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-tert-Butylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Fluorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;

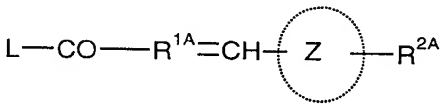
E-N-(4-Methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Carbomethoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl) acrylamide;
E-N-(4-Cyanophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Nitrophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(4-Methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-N-(3-Methoxy-5-trifluoromethylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)acrylamide;
E-1-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone;
E-1-(3,4-Dihydro-2H- quinolin-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone;
E-1-(3,3-Dimethyl-2,3-dihydroindol-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone, and;
E-1-(2,3-Dihydroindol-1-yl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)propenone.

7. A process for the preparation of compounds of formula (I), which comprises
(a). for compounds of formula (I) in which P is -NH- and Q is $-CR^1=CH-$, reacting a compound of formula (II)



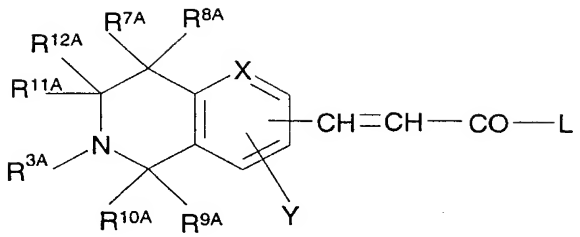
(II)

with a compound of formula (III)



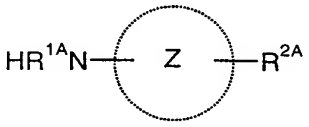
(III)

or,
(b) for compounds of formula (I) in which P is -CH=CH- and Q is $-NR^1-$, reacting a compound of formula (IV)



(IV)

with a compound of formula (V)



(V)

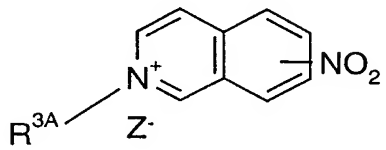
where R^{1A}, R^{2A}, R^{3A}, R^{7A}, R^{8A}, R^{9A}, and R^{10A} are independently R^1, R^2, R^3, R^7, R^8, R^9, and R^{10} as defined for formula (I) or a group or groups convertible thereto; Z, X and Y are as defined for formula (I); and L is OH or a halogen;

and where required converting an R^{1A}, R^{2A}, R^{3A}, R^{7A}, R^{8A}, R^{9A}, or R^{10A} group to an R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group;

converting one R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group to another R^1, R^2, R^3, R^7, R^8, R^9, or R^{10} group;

converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

8. A compound of formula (XII)



(XII)

wherein R^{3A} is R^3 as defined in claim1 or a group convertible thereto and M is a leaving group such as halogen, especially iodo, or tosylate.

9. A pharmaceutical composition for use in the treatment and/or prevention of anxiety, mania, depression , panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects

associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

10. A method of treatment and/or prevention of anxiety, mania, depression , panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof.

11. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of anxiety, mania, depression , panic disorders and/or aggression, disorders associated with a subarachnoid

haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

12. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prevention of anxiety, mania, depression , panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/05583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D217/04 C07D471/04 A61K31/472 A61K31/4725 A61K31/4375
C07D405/12 C07D409/12 C07D401/12 C07D217/06 C07D217/02
C07D413/12 C07D401/06 //(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATHISON I W ET AL: "SYNTHESIS AND HYPOTENSIVE PROPERTIES OF TETRAHYDROISOQUINOLINES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 16, no. 4, page 332-336 XP002040786 ISSN: 0022-2623 see page 332,scheme1 and page 334 experimental section	8
A	the whole document	1,9
A	GB 1 164 192 A (FARBWERKE HOECHST AG) 17 September 1969 (1969-09-17) page 1, line 6 - line 8; claims 2,17	
A	WO 97 48683 A (SMITHKLINE BEECHAM PLC) 24 December 1997 (1997-12-24) claims	1,9-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1999	29/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. national application No.
PCT/EP 99/05583

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/EP 99/05583

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